AstraZeneca

Briefing Document	
Drug substance	Naloxegol
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Naloxegol

NDA 204-760

Briefing Document for the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

1. INTRODUCTION

AstraZeneca has submitted a New Drug Application for naloxegol, a peripheral μ-opioid receptor antagonist, to the Food and Drug Administration (FDA) for the following proposed indication: *naloxegol is indicated for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain*. AstraZeneca has applied to market naloxegol 25 mg and 12.5 mg tablets.

The FDA indicated to sponsors their desire to hold an advisory committee that would focus predominantly on safety, to help FDA to determine what guiding principles are needed to decide that a premarketing safety database is sufficient for approval of peripheral μ-opioid antagonists, and if it is not sufficient what additional studies would be required. They invited the sponsors with peripheral μ-opioid antagonist compounds to present available data to inform the Advisory Committee discussion on 4 topics:

1. Pharmacology of their product (nonclinical receptor affinity, bioavailability and organ distribution, clinical pharmacokinetic profile, and pharmacodynamic effects)/gut selectivity (Section 5)

2. Potential to produce opioid withdrawal (OWD; Section 6)

3. Potential link between OWD and cardiovascular (CV) effects (Section 7)

4. Other potential physiological link(s) between opioid antagonists and CV effects (Section 8)

Based on FDA recommendation, this Briefing Book focuses on these 4 topics and also includes an overall assessment of CV safety.

2. EXECUTIVE SUMMARY

2.1 Background

Naloxegol is a polyethylene glycol (PEG) derivative of naloxone designed to have limited ability to cross the blood-brain barrier (BBB) while targeting μ-opioid receptors in the periphery to directly and specifically address the causes of opioid-induced constipation (OIC). AstraZeneca conducted the naloxegol Phase III program in patients with OIC in accordance with advice received in 2010 and 2011 from the United States Food and Drug Administration (FDA) and European Union Committee for Medicinal Products for Human Use. Upon completion of the naloxegol Phase III studies in 2012, the FDA raised a concern that there could be a possible class effect of μ-opioid receptor antagonists precipitating opioid withdrawal (OWD) and potentially resulting in cardiovascular (CV) adverse events (AEs). The FDA stated that another μ-opioid receptor antagonist "has been associated with a higher number of ischemic CV events compared to placebo in a 12-month study in patients with opioid bowel dysfunction" (alvimopan Study GSK 014, reviewed at the 23 January 2008 FDA

Advisory Committee meeting). In addition, the FDA stated that "in post-marketing safety evaluations (from July 2011 through December 2011), AEs of drug withdrawal syndrome were reported with the use of methylnaltrexone."

OIC is a burdensome and common side effect of opioid therapy, which does not improve over time with symptoms persisting throughout the duration of opioid use (Warner 2012). Most side effects associated with opioids subside with chronic use; however, tolerance to constipation does not typically develop with OIC (Panchal et al 2007, Benyamin et al 2008).

Unrelieved constipation symptoms may add to the burden of pain and underlying illness and may dissuade patients from using the required analgesic dose to achieve effective pain relief (Camilleri 2011). OIC may interfere with activities of daily living, resulting in a lower quality of life. Furthermore, a recent 500 patient survey concluded that OIC significantly impacts pain management with regards to adherence and compliance of prescribed opioid therapy in patients with non-cancer pain (Datto et al 2014, Daniell 2011). The need for new and effective therapies is especially apparent for patients who continue to have constipation symptoms despite treatment with laxatives (Becker and Blum 2009, Bell et al 2009, Mitchell et al 2004, Müller-Lissner et al 2013). Naloxegol targets the underlying causes of OIC by binding to μ-opioid receptors within the gastrointestinal (GI) tract. With its limited ability to affect opioid receptors located in the central nervous system (CNS) at therapeutic doses, naloxegol has been shown to alleviate OIC without reducing the central analgesic effects of opioids.

2.2 Naloxegol clinical data

The naloxegol clinical program was designed to assess naloxegol efficacy and general safety in patients with OIC, which included 1497 patients who took naloxegol in Phases II and III, for a total exposure of 624 patient-years. The Phase III program consisted of 4 studies in patients with non-cancer pain: 2 identical placebo-controlled, double-blind, 12-week efficacy and safety studies of naloxegol 12.5 mg and 25 mg (Studies Kodiac 4 [K4] and Kodiac 5 [K5]); a 12-week, placebo-controlled, double-blind, rollover safety extension study following Study K4 (Study Kodiac 7 [K7]); and a randomized, 52-week, open-label, parallel-group, long-term safety study of naloxegol 25 mg with a Usual Care control arm (Study Kodiac 8 [K8]). For further details, see Sections 3.1 and 3.2.

The Phase III program was not designed or powered to rule out differences or increased risk for rare or infrequent safety events. However, it did include a comprehensive assessment of both CV safety (including blinded, independent adjudication of all deaths, CV serious adverse events [SAEs], and CV events of interest) and the potential risk of OWD and reversal of analgesia, as well as prospectively monitored endpoints, including vital signs and electrocardiogram (ECG) measurements, allowing the safety and tolerability profile of naloxegol to be well characterized.

2.2.1 Efficacy of naloxegol

Naloxegol 25 mg demonstrated a statistically significant improvement over placebo for the primary endpoint, response over 12 weeks (10 to 15 percentage points), and all multiplicity–

protected secondary endpoints (response rate for laxative inadequate responders, time to first post-dose spontaneous bowel movement [SBM], and number of days per week with a minimum of 1 SBM). The response was defined as ≥3 SBMs per week with at least 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks. The effect was consistent and durable over 12 weeks.

The naloxegol 12.5 mg dose demonstrated statistical significance for the primary endpoint and key secondary endpoints versus placebo in 1 of the 2 studies (Study K4). In Study K5, a trend in favor of 12.5 mg was observed, but the primary endpoint did not achieve statistical significance compared to placebo. Although the 12.5 mg dose did not demonstrate replicated statistically significant improvements, results of secondary endpoints in both studies support that the 12.5 mg dose is biologically active and, as such, it may offer benefit to some patients. For further details, see Section 3.4.

2.2.2 General safety of naloxegol

Naloxegol was found to be generally safe and well tolerated for up to 52 weeks of treatment. In the pivotal 12-week studies (Studies K4 and K5), the incidence of SAEs was balanced across treatment groups, while the incidence of AEs and the incidence of discontinuation of investigational product due to an AE (DAEs) were higher in the naloxegol 25 mg group than in both the 12.5 mg and placebo groups. Most AEs were mild to moderate in intensity. Results in the 52-week long-term safety Study K8 were similar. There were a total of 7 deaths in the naloxegol clinical program. None of the 7 deaths were assessed by the Investigator as related to naloxegol. There was 1 death reported in a Phase I renal impairment study, 35 days after last dose. A total of 6 deaths occurred in the Phase II and III studies: 1 was in the placebo/Usual Care groups (0.1%) in the controlled 52-week long-term safety study, 3 were in the naloxegol 12.5 mg group (0.7%), and 2 were in the naloxegol 25 mg group (0.2%). No common etiology was identified for these deaths. For further detail, see Section 3.5.1.

The higher incidence of AEs and DAEs in the naloxegol 25 mg group was primarily due to GI AEs (the most common of which were abdominal pain, diarrhea, nausea, and flatulence), which was expected based on the mechanism of action (MoA) of naloxegol. In the 12-week placebo-controlled pool, the incidences of these AEs in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively, were abdominal pain (5.6%, 9.8%, and 15.9%), diarrhea (4.3%, 5.7%, and 9.2%), nausea (4.5%, 6.6%, and 8.1%), and flatulence (2.5%, 2.9%, and 5.8%). The prevalence of the most common GI AEs decreased over the course of treatment. For further details, see Section 3.5.2.

2.2.3 Naloxegol CV safety

The overall nonclinical CV safety assessment did not reveal any major effects on measured CV parameters at clinically relevant exposures. A battery of nonclinical tests supported the absence of any direct effects of naloxegol on the CV system. In a single-dose dog telemetry study, a decrease in arterial blood pressure, left ventricular systolic pressure, and indices of cardiac contractility and an increase in HR were noted at exposures at least 6.7× higher than those achieved in the clinical studies at the proposed 25 mg dose. No effects were seen on electrophysiological or hemodynamic CV parameters in repeat-dose toxicity studies in the dog (up to 9 months; at least 66× higher than human maximum plasma drug concentration [C_{max}] at the proposed 25 mg dose), and the hemodynamic changes seen in the single-dose dog telemetry study were not seen in the clinical studies. For further details, see Section 4.2.

In Phase I clinical safety studies, single doses of up to 1000 mg and repeated doses of 500 mg/day showed no evidence of CV effects in healthy volunteers. A thorough QT study, using naloxegol 25 mg (therapeutic dose) and naloxegol 150 mg (supra-therapeutic dose), showed that naloxegol did not prolong the placebo-corrected, baseline-adjusted, Fridericia QT interval; the upper bound of the 2-sided 90% confidence intervals (CIs) were below 10 ms at all time points post-dose. For further details, see Section 4.2.

CV events were defined as a topic of special interest in the Phase III program because of findings in the dog telemetry study and a potential CV safety signal (myocardial ischemia) reported from a long-term safety study of alvimopan in patients with opioid bowel dysfunction (Study GSK 014). An independent, external Cardiovascular Event Adjudication Committee reviewed all deaths and CV SAEs and CV AEs of potential interest (Section 4.3.1). Predefined CV events of primary interest for adjudication included “major adverse cardiovascular event (MACE)” (CV death, myocardial infarction [MI], and stroke) as well as CV events leading to hospitalization for heart failure or unstable angina. Additional safety assessments included a 4-hour observation period after the first dose of investigational product, with data collection at approximately the time of C_{max} (sparse pharmacokinetic [PK] sampling, 1-hour post-first-dose vital signs measurements, and 2-hour post-first-dose ECG). For further details, see Section 4.3.

Over two-thirds of the patients in the Phase III population had at least 1 CV risk factor, and over 40% of the patients had a history of CV disease, diabetes, or ≥2 CV risk factors. For further details, see Section 3.3.

The overall incidence of CV SAEs and adjudicated MACE was low and similar across treatment groups both in the placebo-controlled studies and in the randomized, long-term safety study (Table 1). For further details on MACE, see Section 4.3.2. For details on CV SAEs, see Section 4.3.3.

Table 1 CV/cerebrovascular SAEs or adjudicated MACE in Phase III (placebo-controlled pool and Study K8)

	Placebo-controlled pool (Studies K4/K7 and K5)			52-week safety study (Study K8)	
Category	**Placebo (N=444)**	**NGL 12.5 mg (N=441)**	**NGL 25 mg (N=446)**	**Usual Care (N=270)**	**NGL 25 mg (N=534)**
SAEs (cardiac SOC, vascular SOC, and cerebrovascular SMQs)	**5 (1.1%)**	**6 (1.3%)**	**7 (1.5%)**	**6 (2.2%)**	**5 (0.9%)**
Any MACE per CV-EAC	**2 (0.5)**	**2 (0.5)**	**1 (0.2)**	**2 (0.7)**	**2 (0.4)**
CV death	0	2 (0.5)	0	1 (0.4)	1 (0.2)
Acute MI	2 (0.5)	1 (0.2)	1 (0.2)	0	1 (0.2)
Stroke	0	0	0	1 (0.4)	0

CV Cardiovascular; CV-EAC Cardiovascular Event Adjudication Committee; MACE Major adverse cardiovascular event; MedDRA Medical Dictionary for Regulatory Activities; MI Myocardial infarction; N Total number of patients; NGL Naloxegol; SMQ Standard MedDRA query; SAE Serious adverse event; SOC System organ class.

The MI rates per 100 patient-years of exposure seen in the naloxegol treatment groups (0.45, 95% CI: 0.09, 1.32) are within the range of background event rates for MI among chronic opioid users without a history of MI (ie, excluding patients with an MI within the past 6 months, Carman et al 2011; and excluding patients with an MI within the past 18 months, LoCasale 2013), in which MI rates per 100 patient-years of exposure were 0.60 (95% CI: 0.57, 0.64) and 0.83 (95% CI: 0.69, 1.00), respectively (Table 10). For further details, see Section 4.3.2.

Mean changes from baseline in vital signs and the pattern or frequency of vital signs outliers were similar across the treatment groups. In addition, the proportion of patients meeting established criteria for hypertension was similar across treatment groups. Rate pressure product changes from baseline in the 12 week studies and the long-term safety study were similar across treatment groups. For further details, see Section 4.3.5.

2.3 Pharmacology of naloxegol

Naloxegol is a PEG derivative of naloxone with limited ability to cross the BBB. Pegylation confers 3 beneficial properties for naloxegol when compared to naloxone: (1) naloxegol has reduced passive permeability across membranes, (2) naloxegol is a P-glycoprotein (P-gp) efflux transporter substrate, and (3) it allows for oral bioavailability. The first 2 properties work together to reduce passive permeability/transport across the BBB and limit entry into the CNS compared with naloxone.

Naloxegol has high affinity for μ-opioid receptors (binding affinity [K_i]: 7.42 nM) and κ-opioid receptors (K_i: 8.65 nM) and has low affinity for δ-opioid receptors (K_i: 203.0 nM). Naloxegol exposures at 25 mg are sufficient to antagonize μ-opioid receptors, as well as κ-opioid receptors, but are unlikely to antagonize δ-opioid receptors. For further details on receptor binding, see Section 5.1.

Naloxegol is characterized by rapid absorption with peak plasma concentrations attained in less than 2 hours, dose-proportional exposure from 8 mg to 1000 mg, mean terminal elimination half-life values of approximately 10 hours at therapeutic doses, steady state achieved within 2 to 3 days following multiple dosing, and minimal accumulation with once daily dosing. The primary route of naloxegol elimination is via hepatic metabolism, with renal excretion playing a minimal role. The absolute bioavailability in man has not been determined. The PK of naloxegol is affected by food and cytochrome P450 3A4/P-gp modulators. For details on PK properties of naloxegol, see Section 5.2.

In healthy volunteers, assessments of peripheral and central μ-opioid receptor antagonism via morphine-induced delay in orocecal transit time and morphine-induced miosis indicated that naloxegol at doses from 15 mg to 125 mg antagonizes peripheral opioid effects on the GI tract without antagonizing opioid effects on the CNS. At doses >125 mg, possible partial reversal of morphine-induced miosis was observed in 2 of 17 subjects (1 who received naloxegol 250 mg and 1 who received naloxegol 1000 mg). For details, see Section 5.3.

Review of publicly available data indicates that there are differences among peripherally acting μ-opioid receptor antagonists (PAMORAs) related to chemical structure, circulating active metabolites, and receptor subtype binding and selectivity (for details, see Section 5.4).

2.4 Potential of naloxegol to produce OWD

OWD syndrome consists of a cluster of non-specific symptoms, often described as a flu-like, non-life-threatening illness. OWD is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a constellation of 3 or more withdrawal symptoms developing within minutes to several days after cessation of prolonged opioid use or administration of a centrally acting opioid antagonist after a period of opioid use. OWD syndrome is considered to be primarily related to centrally mediated mechanisms. In the instances in which OWD is precipitated by an opioid antagonist, such as intravenous naloxone, the constellation of symptoms is considered to result from the antagonist entering the CNS and displacing the opioid from its receptor. However, both peripheral and central μ-opioid receptors are thought to be involved in the manifestation of the full syndrome.

In the clinical program in OIC, naloxegol demonstrated a low propensity to produce OWD syndrome. In the Phase III studies, the treatment groups were similar with regard to OWD scores (as measured using the modified Himmelsbach scale), pain scores (as measured using the Numeric Rating Scale), or in opioid use between the naloxegol and comparator groups. However, in rare cases (approximately 1%), a constellation of GI and non-GI symptoms, identified by the Investigator as OWD, was reported. Due to the MoA of naloxegol, and its pharmacodynamic and physiologic effects (reversal of impaired GI motility and decreased intestinal fluid absorption), GI side effects are expected in some patients. These OWD AEs reported in the Phase III studies were observed shortly after initial administration, were more common in the naloxegol 25 mg group than in either the naloxegol 12.5 mg or placebo groups, and were not associated with serious medical sequelae. Details are provided in Section 6.

In the naloxegol Phase III program, a total of 13 withdrawal events were reported by Investigators, with more reports observed in the naloxegol 25 mg group (9 patients, 0.9%) than in the comparator (placebo or Usual Care; 1 patient, 0.1%) or naloxegol 12.5 mg (3 patients, 0.7%) groups. All 13 cases were reviewed post hoc, and of these, 7 cases were considered attributable to treatment with investigational product (0.1%, 0.2%, and 0.5% for the placebo/Usual Care, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively); all 5 cases reported for the 25 mg group were noted to have GI symptoms at the time of the OWD (eg, diarrhea, vomiting, abdominal pain, and abdominal cramping) and various other non-GI symptoms. For further details, see Section 6.3.

A post hoc computer-based search of the safety database for cases with 3 or more concurrently occurring AEs listed in the DSM-5 as a symptom of OWD was conducted. This analysis identified 6 additional potential cases, not including those mentioned above (2 cases on naloxegol 12.5 mg and 4 cases on naloxegol 25 mg). Consistent with the Investigator-reported OWD AEs, results of this post hoc analysis showed the DSM-5-based events to be uncommon but occur more frequently with naloxegol than with placebo. For further details, see Section 6.4.

2.5 Potential links between OWD and CV events

The naloxegol Phase III data were reviewed for any association between patients who had potential OWD events and CV effects. Data for all patients with Investigator-reported OWD or who met DSM-5 criteria for OWD in a post hoc analysis, or who had MACE, CV SAEs, or CV AEs were reviewed. Of the 9 cases of MACE, none occurred in any of the 13 patients with Investigator-reported OWD or in any of the 6 additional patients who met the DSM-5 criteria. In addition, it is important to note that none of the patients with OWD AEs or who met DSM-5 criteria had CV AEs. For further information, see Section 7.

2.6 Other potential physiological links between opioid antagonists and CV effects

MACE can occur from multiple mechanisms, including myocardial ischemia from increased oxygen demand, enhanced atherogenesis, electrolyte disorders, and salt and/or water retention. The naloxegol development program was not designed to specifically rule out all these mechanisms. Indirect evidence generated in the naloxegol program related to these possible triggering mechanisms does not indicate an increased CV risk in the intended population. For further information, see Section 8.

2.7 Summary

Based on the available data from the naloxegol clinical program designed to assess naloxegol efficacy and general safety in patients with OIC:

- The incidence of MACE, CV SAEs, CV AEs, and abnormal vital signs was low and similar across the treatment groups in the Phase III clinical program.
- Naloxegol has a low propensity to produce OWD syndrome. No association was seen between CV events and OWD. There were no patients with an OWD event (either Investigator-reported OWD or post hoc DSM 5 case) who had MACE, CV SAEs or AEs, or a syncope event.
- Extensive clinical and post-marketing experience with μ-opioid receptor antagonists (eg, naltrexone and naloxone, although for indications other than OIC) reveals that serious CV events with these compounds are rare.
- Naloxegol is a PEG derivative of naloxone with limited ability to cross the BBB.
- While the MoA for naloxegol is the same as other PAMORAs, there are differences in chemical structure, circulating active metabolites, and receptor binding and selectivity, which warrants that, for approval, each PAMORA should be independently evaluated for benefit-risk ratio, including potential CV risk.
- Limited indirect evidence generated in the naloxegol program related to possible triggering mechanisms for MACE does not indicate a plausible mechanism for increased CV risk in the intended population.

The naloxegol clinical CV data appear to be different from the alvimopan long-term safety data, referenced by the FDA, even though neither dataset was powered for precisely estimating rare events. The reasons for these differences are not known but may be due to a chance imbalance observed in a small numbers of events and/or other unknown confounding differences in trial design or conduct. Alternatively, differences in clinical outcomes between alvimopan and naloxegol could be the consequence of differences in structure, metabolism, and/or differences in opioid subtype receptor binding and selectivity between the molecules. Based on the totality of the information available, including nonclinical and clinical naloxegol cardiac safety data, a lack of a plausible biological mechanism, and additional analyses done to address the FDA's specific questions, AstraZeneca concludes that naloxegol treatment is unlikely to increase the CV risk among patients with OIC. Therefore, AstraZeneca concludes that the safety of naloxegol has been sufficiently characterized for approval.

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3. NALOXEGOL CLINICAL DATA

3.1 Naloxegol clinical program

The clinical development program was designed to support the registration of naloxegol for the treatment of opioid-induced constipation (OIC). Four Phase III studies for non-cancer-related pain were completed, including:

- 2 identical placebo-controlled, double-blind, 12-week Phase III pivotal efficacy and safety studies, Kodiac 4 and Kodiac 5 (referred to hereafter as Study K4 and Study K5);
- a 12-week, placebo controlled double-blind, rollover safety extension study following Study K4, Kodiac 7 (Study K7); and
- a randomized, 52-week, open-label, parallel-group, long-term safety study with a Usual Care control arm, Kodiac 8 (Study K8).

The selection of the 25 mg naloxegol dose in the Phase III program was supported by a single Phase II study in patients with OIC. The 12.5 mg dose was included to test for the lowest effective dose and was supported by pharmacometric modeling of the Phase II data. Additionally, 14 Phase I studies investigated the biopharmaceutics and clinical pharmacology of naloxegol in 438 volunteers, including 24 subjects with varying degrees of hepatic impairment and 16 subjects with varying degrees of renal impairment.

Across the Phases II and III clinical programs, naloxegol was studied in 1497 patients with OIC who took naloxegol, for a total exposure of 624 patient-years. Of these, 537 patients had at least 24 weeks of exposure and 330 patients had at least 50 weeks of exposure.

3.2 Phase III program design

The naloxegol Phase III program was designed to assess naloxegol efficacy and general safety in patients with OIC. The program was not designed or powered to rule out differences or increased risk for rare or infrequent safety events. However, the program included a comprehensive assessment of both cardiovascular (CV) safety (including blinded, independent adjudication of all deaths, CV serious adverse events [SAEs], and CV events of interest; see Section 4.3.1 for details on the adjudication process) and the potential risk of opioid withdrawal (OWD). In addition, the program included prospective monitoring endpoints, such as vital signs and electrocardiogram measurements at 1 hour post-dose and every subsequent visit, along with evaluation of the potential risk of OWD and reversal of analgesia to characterize the safety and tolerability profile of naloxegol.

A study flow chart for the pivotal studies (Studies K4 and K5) and the controlled, long-term safety study (Study K8) are shown in Figure 1 and Figure 2. Ten percent of the patients in Study K8 rolled over from Studies K5 and K7 before being re-randomized; newly randomized patients accounted for 90% of the patients in Study K8. In the Phase III studies, patients were administered naloxegol in the morning, approximately 1 hour before eating. In all studies, patients completing a study were followed up for 2 weeks after treatment discontinuation. Patients discontinuing the study for any reason were required by protocol to have a final follow-up visit following withdrawal from the study but were not required to be followed up until the planned study completion.

Figure 1 Study flow chart for Studies K4 and K5 (12-week treatment period)

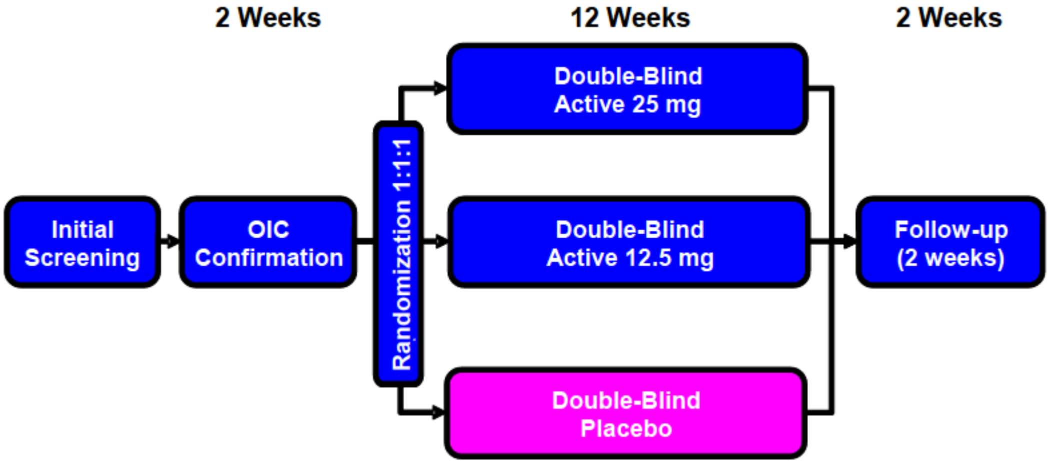
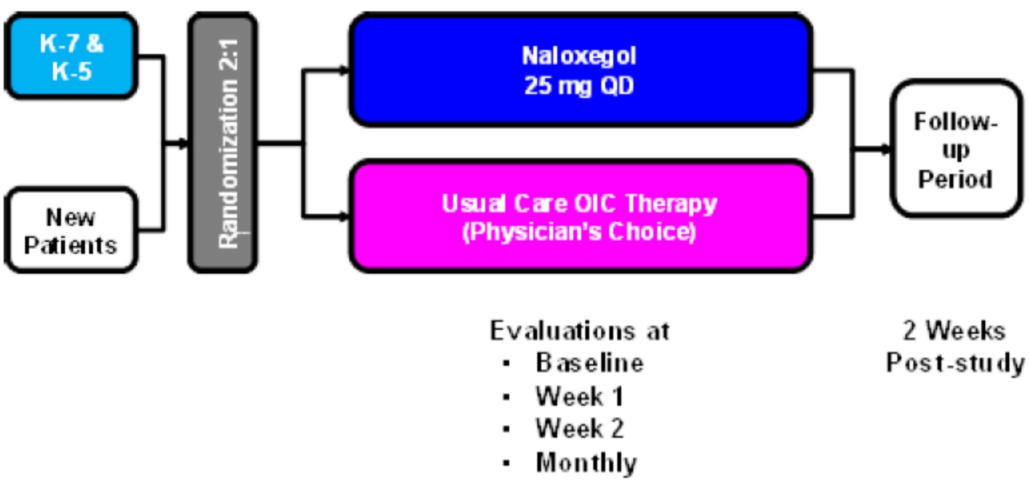


Figure 2 Study flow chart for Study K8 (52-week treatment period)



OIC Opioid-induced constipation; QD Once daily.

The studies enrolled adult patients whose OIC diagnosis had been confirmed prospectively with a 2-week daily diary, who were receiving a stable maintenance opioid regimen of at least 30 morphine equivalent units for non-cancer-related pain, and who reported a history of <3 spontaneous bowel movements (SBMs) per week and at least 1 OIC-associated symptom at screening. The randomization procedure in the pivotal studies was designed to ensure that at least 50% of the patients randomized had an inadequate response to laxatives (characterized as having continued moderate to very severe OIC symptoms despite current laxative use) to allow investigation of efficacy in this particular subgroup.

The pivotal studies excluded certain patient populations to minimize confounding factors in assessment of the treatment effect and/or to avoid putting the patient at undue risk. These included patients with:

- pre-existing constipation for reasons other than opioid treatment, or patients who had diarrhea
- potential loss of integrity of the gastrointestinal (GI) wall, due to risk for bowel perforation
- a requirement for certain concomitant medications (ie, strong inhibitors of cytochrome P450 3A4 or P-glycoprotein, opioid antagonists and mixed agonists/antagonists, and laxatives)
- potential for blood-brain barrier disruptions (eg, active multiple sclerosis, advanced Alzheimer's disease, and uncontrolled epilepsy)
- cancer pain
- CV exclusions, including (Text in *italics* was amended following the results from the thorough QT study. Note that over half of the patients in Studies K4 and K5 were randomized after implementation of Clinical Study Protocol Amendment 2, which relaxed cardiac exclusion and discontinuation criteria related to risk for ventricular arrhythmia.):
    – Patients who *were at increased risk for ventricular arrhythmia, including those who had a prior history of serious ventricular arrhythmia, family history of sudden cardiac death, family history of long QT syndrome,* had a recent history of myocardial infarction (MI) within 6 months before randomization, had overt CV disease (eg, symptomatic heart failure), had a prolonged repeat Fridericia QT interval (QTcF) *(QTcF >450 ms at screening, confirmed by repeat QTcF on electrocardiogram taken within 5 minutes)*, or were on medications that prolong the QT/corrected QT interval.
    – Patients who had a QTcF >500 ms at screening, had a recent history of MI within 6 months before randomization, had symptomatic congestive heart failure, or had any other overt CV disease.

3.3 Naloxegol Phase III population baseline characteristics

Throughout this Briefing Book, specific patient identifier information has been excluded (eg, the ages of patients are presented as 5-year age ranges) to comply with Health Insurance Portability and Accountability Act privacy requirements.

An overview of demographic and other patient characteristics for Studies K4 and K5 is presented in Table 2. Patient demographics and other patient characteristics in Study K8 (Appendix Table 22) were similar to those seen in Studies K4 and K5.

Table 2 Demographic characteristics, Studies K4 and K5 (ITT analysis set)

	Study K4			Study K5		
Demographic characteristics	**Placebo (N=214)**	**Naloxegol 12.5 mg (N=213)**	**Naloxegol 25 mg (N=214)**	**Placebo (N=232)**	**Naloxegol 12.5 mg (N=232)**	**Naloxegol 25 mg (N=232)**
Age, mean (SD) years	52.9 (9.99)	51.9 (10.43)	52.2 (10.29)	52.3 (11.62)	52.0 (11.02)	51.9 (12.11)
Sex, n (%)						
Male	74 (34.6)	78 (36.6)	96 (44.9)	87 (37.5)	83 (35.8)	85 (36.6)
Female	140 (65.4)	135 (63.4)	118 (55.1)	145 (62.5)	149 (64.2)	147 (63.4)
Race, n (%)						
White	160 (74.8)	164 (77.0)	173 (80.8)	183 (78.9)	187 (80.6)	189 (81.5)
Black or African American	44 (20.6)	42 (19.7)	38 (17.8)	44 (19.0)	41 (17.7)	40 (17.2)
Asian	4 (1.9)	5 (2.3)	1 (0.5)	0	1 (0.4)	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	1 (0.4)
American Indian or Alaska Native	2 (0.9)	1 (0.5)	0	2 (0.9)	1 (0.4)	1 (0.4)
Other	4 (1.9)	1 (0.5)	2 (0.9)	3 (1.3)	2 (0.9)	1 (0.4)
BMI ≥30 kg/m^2, n (%)	106 (49.5)	114 (53.5)	111 (51.9)	111 (47.8)	106 (45.7)	115 (49.6)
Primary reason for pain, n (%)						
Back pain	118 (55.1)	131 (61.5)	110 (51.4)	129 (55.6)	136 (58.6)	130 (56.0)
Joint pain	7 (3.3)	8 (3.8)	7 (3.3)	10 (4.3)	11 (4.7)	16 (6.9)
Fibromyalgia	15 (7.0)	6 (2.8)	9 (4.2)	18 (7.8)	16 (6.9)	11 (4.7)
Mean (SD) duration of current opioid use, months	39.5 (39.35)	44.4 (47.31)	44.5 (47.82)	43.0 (51.39)	48.5 (48.66)	40.9 (41.56)
Daily maintenance opioid dose (meu)[a], mean (SD)	135.6 (145.80)	139.7 (167.39)	143.2 (150.07)	119.9 (103.75)	151.7 (153.02)	136.4 (134.31)
Patient took a laxative over the past 2 weeks, n (%)	151 (70.6)	140 (65.7)	166 (77.6)	173 (74.6)	156 (67.2)	166 (71.6)
Numeric Rating Scale scores at baseline, mean (SD)	4.5 (1.85)	4.8 (1.69)	4.7 (1.59)	4.6 (1.82)	4.6 (1.87)	4.6 (1.65)

a Values are based on the safety analysis set.

BMI Body mass index; ITT Intent-to-treat; meu Morphine equivalent units; N Total number of patients; n Number of patients in category; SD Standard deviation.

A post hoc assessment of baseline patient-level CV risk was conducted. Over two-thirds of the patients in the Phase III population had at least 1 CV risk factor, and over 40% of the patients had a history of CV disease, diabetes, or ≥2 CV risk factors (Table 3).

Table 3 Summary of baseline CV risk factors (Studies K4, K5, and K8)

	Percent of patients				
	12-week pool (Studies K4 and K5)			Study K8	
	Placebo (N=444)	Naloxegol 12.5 mg (N=441)	Naloxegol 25 mg (N=446)	Usual Care (N=270)	Naloxegol 25 mg (N=534)
CV characteristic					
Age ≥65 years	11.3	10.0	11.9	13.7	9.9
Male	35.8	36.3	40.6	33.7	33.9
History CV disease	11.9	12.9	13.7	14.1	11.8
History of diabetes	18.0	17.7	17.3	19.3	16.1
History of hypertension	49.8	46.3	53.1	52.6	48.1
History of dyslipidemia	38.3	36.3	40.6	37.8	40.6
Smoking	6.1	5.9	7.8	5.9	7.3
Use of CV, hypertension, or hyperlipidemia medications	52.0	49.4	56.7	50.7	51.7
CV risk classes[a]					
Diabetes, history of CV disease, or ≥2 other risk factors	39.9	40.1	44.4	40.0	40.1
One risk factor (excluding diabetes and history of CV disease)	29.3	26.3	24.7	30.0	27.2
No risk factor	30.9	33.6	30.9	30.0	32.8

[a] Post hoc classification of CV risk at baseline (White et al 2002, Wilson et al 1998) based on the following risk factors: age >75 years, hypertension or on hypertensive medication, hyperlipidemia or use of lipid-lowering medication, current smoker, use of low-dose aspirin for a CV-related indication, diabetes, and prior history of CV disease.

Note: Smoking status was not routinely collected in these studies.

CV Cardiovascular disease; N Total number of patients.

Demographic characteristics, source of pain, body mass index (BMI), and prior CV risk factors in Studies K4 and K5 and Study K8 were consistent with other clinical studies in this population and representative of patients with OIC or with patients taking opioids chronically for non-cancer pain (Braden et al 2008, Cicero et al 2009, Hudson et al 2008, Coyne et al 2013, Carman et al 2011). Specifically, a multi-country prospective observational study of patients with OIC reported that 62% of participants were female with a mean age of 52.6 years and a majority (85%) were Caucasian (Coyne et al 2013). This consistency extended into chronic opioid users for non-cancer pain with the majority of patients being female (range: 59% to 72%), Caucasian (88%), and with a mean age ranging from 50 to 57 years (Braden et al 2008, Cicero et al 2009, Hudson et al 2008). Additionally, among patients with OIC, mean BMI was 29.7 kg/m^2 and the large majority received their opioid therapy for back pain (77%) (Coyne et al 2013). For CV risk factors, a prior history of hypertension and diabetes mellitus was observed in 28% and 10% of patients with OIC, respectively (Coyne et al 2013). Among chronic opioid users with non-cancer pain, survey and claims studies reported baseline hypertension (range: 30% to 43%), coronary heart disease (6%), angina/heart failure (range: 4% to 12%), arrhythmia (4%), stroke/transient ischemic attack (2%), diabetes (12%), and hyperlipidemia/hypercholesterolemia (range: 21% to 29%; Cicero et al 2009, Hudson et al 2008, Coyne et al 2013, Carman et al 2011).

In summary, the patient population in the naloxegol Phase III program was consistent with the target population.

3.4 Naloxegol efficacy in the Phase III program

The primary endpoint in the pivotal studies was recommended by the Food and Drug Administration (FDA) and was multifactorial, ensuring patients had to demonstrate a clinically relevant improvement in SBM frequency, which was durable and maintained across the 12-week treatment period. To be considered a responder, patients had to have ≥3 SBMs per week with at least 1 SBM/week increase over baseline for at least 9 of the 12 treatment weeks and for 3 of the last 4 treatment weeks. Requiring all 3 of these criteria assures that patients classified as responders have demonstrated a clinically relevant and sustained improvement throughout the 12 weeks of treatment.

In the Phase III pivotal efficacy studies, naloxegol 25 mg demonstrated a statistically significant improvement over placebo for the primary endpoint (10- to 15-percentage points; Table 4) and all multiplicity–protected secondary endpoints (Table 5). The effect was consistent and durable over 12 weeks. The direction of treatment effect for the naloxegol 25 mg groups compared with placebo was consistent across all prespecified subgroups, including the laxative inadequate responder subgroup.

The lower dose, naloxegol 12.5 mg, demonstrated statistical significance for the primary endpoint and key secondary endpoints versus placebo in 1 of the 2 studies (Study K4). In the other study, Study K5, a trend in favor of the 12.5 mg group was observed, but the primary endpoint did not achieve statistical significance compared to placebo, and as such, for the 12.5 mg dose compared to placebo, significance could not be claimed for any of the multiplicity-protected secondary endpoints under the prespecified multiple testing procedure, even though 2 of these endpoints showed separation from placebo, with unadjusted p-values <0.001.

Professional societies and health authorities have not defined a clinically relevant treatment effect versus placebo in OIC. However, there is a recent precedent for this condition: the FDA approved the first oral OIC-specific therapy, lubiprostone (AMITIZA®) in April 2013. Results from these studies showed responder rates of 27.1% for lubiprostone and 18.9% for placebo, a treatment difference of 8.2%, using a 12-week SBM responder primary endpoint (AMITIZA Prescribing Information 2013).

Table 4 Primary endpoint: CMH analysis of response rate for Weeks 1 to 12, Studies K4 and K5 (ITT analysis set)

	Study K4			Study K5		
	Placebo (N=214)	Naloxegol 12.5 mg (N=213)	Naloxegol 25 mg (N=214)	Placebo (N=232)	Naloxegol 12.5 mg (N=232)	Naloxegol 25 mg (N=232)
N	214	213	214	232	232	232
Number (%) of patients responding	63 (29.4)	87 (40.8)	95 (44.4)	68 (29.3)	81 (34.9)	92 (39.7)
RR (Comparison vs. placebo)[a]	NA	1.380	1.509	NA	1.188	1.348
95% CI	NA	1.062, 1.795	1.168, 1.949	NA	0.911, 1.548	1.045, 1.739
p-value	NA	0.015[b]	0.001[b]	NA	0.202	0.021[b]

[a] Analysis via CMH test stratified by response to laxatives at baseline (LIR, LAR, LUR).
[b] Statistically significant under multiplicity testing procedure.
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.
CI Confidence interval, CMH Cochran Mantel-Haenszel; ITT Intent-to-treat; LAR Laxative adequate responder; LIR Laxative inadequate responder; LUR Laxative unknown responder; N Total number of patients; NA Not applicable; RR Relative risk (a relative risk >1 is indicative of higher response rate on the naloxegol arm).

Table 5 Analyses of the 3 multiplicity-protected secondary endpoints in Studies K4 and K5 (ITT analysis set)

	Study K4			Study K5		
	Placebo (N=214)	**NGL 12.5 mg (N=213)**	**NGL 25 mg (N=214)**	**Placebo (N=232)**	**NGL 12.5 mg (N=232)**	**NGL 25 mg (N=232)**
Response rate for Weeks 1 to 12 in the LIR subgroups[a]						
n	118	115	117	121	125	124
Number (%) of patients responding	34 (28.8)	49 (42.6)	57 (48.7)	38 (31.4)	53 (42.4)	58 (46.8)
RR (comparison vs placebo)[a]	NA	1.479	1.691	NA	1.350	1.489
95% CI	NA	1.038, 2.107	1.25, 2.373	NA	0.967, 1.884	1.078, 2.058
p-value	NA	0.028[b]	0.002[b]	NA	0.074	0.014[b]
Time in hours to first post-dose SBM[c]						
Number of patients (%) with post-dose SBM	209 (97.7)	211 (99.1)	213 (99.5)	228 (98.3)	228 (98.3)	227 (97.8)
Median time (h) to first SBM	35.8	20.4	5.9	37.2	19.3	12.0
Hazard ratio (comparison vs placebo)	NA	1.610	2.384	NA	1.590	1.576
95% CI	NA	1.320, 1.963	1.933, 2.940	NA	1.313, 1.925	1.303, 1.906
p-value	NA	<0.001[b]	<0.001[b]	NA	<0.001	<0.001[b]
Mean number of days per week with at least 1 SBM[d]						
Baseline[e]						
n	213	213	214	232	232	232
Baseline mean (SD)	1.3 (0.85)	1.4 (0.81)	1.2 (0.94)	1.4 (0.89)	1.5 (0.86)	1.3 (0.84)
Change from baseline LS mean (SE)	1.66 (0.13)	2.21 (0.13)	2.48 (0.13)	1.73 (0.12)	2.12 (0.12)	2.41 (0.13)
Difference vs Placebo LS mean	NA	0.55	0.82	NA	0.39	0.68
95% CI	NA	0.24, 0.86	0.51, 1.13	NA	0.09, 0.69	0.37, 0.98
p-value	NA	<0.001[b]	<0.001[b]	NA	0.010	<0.001[b]

[a] Analysis via Chi-squared test.
[b] Statistically significant under multiplicity testing procedure.
[c] Median estimated via Kaplan-Meier technique. Analysis is conducted via log-rank test stratified by response to laxatives at baseline.
[d] Analysis via MMRM with fixed effects for baseline, baseline laxative response, treatment, and treatment time interaction. Study pooled center is included as a random effect.
[e] Baseline based on a patient's mean number of days with SBMs over the OIC confirmation period.
Note: Key secondary endpoints displayed above are included within the multiple testing procedure.
Note: The percentages are based on the number of ITT patients in each treatment group.
CI Confidence interval; ITT Intent-to-Treat; LIR Laxative-inadequate responder/response; LS Least square; MMRM Mixed models for repeated measures; N Total number of patients; n Number of patients in category; NA Not applicable; NGL Naloxegol; OIC Opioid-induced constipation; RR Relative risk (a relative risk >1 is indicative of higher response rate on the naloxegol arm); SBM Spontaneous bowel movement; SD Standard deviation; SE Standard error.

3.5 Adverse events in naloxegol Phase III studies

Safety and tolerability of naloxegol 12.5 mg and 25 mg are established by the 12-week pivotal study pool (Studies K4 and K5), as this provides randomized controlled data versus placebo. Long-term safety (treatment up to 52 weeks) was evaluated by the open-label, randomized, 52-week safety data (Study K8) comparing naloxegol 25 mg versus Usual Care. Naloxegol was found to be generally safe and well tolerated for up to 52 weeks of treatment.

3.5.1 Overall adverse events

In the 12-week pool, the incidence of SAEs was balanced across treatment groups, while the incidence of adverse events (AEs) and the incidence of discontinuation of investigational product due to an AE (DAEs) were higher in the naloxegol 25 mg group than in both the naloxegol 12.5 mg and placebo groups (Table 6). The higher incidence of AEs and DAEs in the naloxegol 25 mg group was primarily related to GI AEs (the most common of which were abdominal pain, diarrhea, nausea, and flatulence). In the long-term safety study (Study K8), the overall AE profile for naloxegol 25 mg (Appendix Table 23) was similar to that observed in the 12-week pivotal studies (Table 7).

There were a total of 7 deaths in the naloxegol clinical program (Appendix Table 26):

- 6 in the Phase II/III studies in patients with OIC (1 in Phase II and 5 in Phase III): 2 on naloxegol 25 mg (0.2%), 3 on naloxegol 12.5 mg (0.7%), and 1 on placebo/Usual Care (0.1%)

- 1 in the Phase I renal impairment clinical pharmacology study in the severe renal impairment group, naloxegol 25 mg.

No common etiology was identified for these deaths. All 5 deaths in the Phase III studies were sent to the Cardiovascular Event Adjudication Committee for adjudication and 4 were adjudicated as a CV death (Section 4.3.2).

Table 6 Number (%) of patients who had ≥1 AE in any category during the treatment period (12-week pool and Study K8)

	12-week pool (Studies K4 and K5)			52-week safety study (Study K8)	
AE category	**Placebo (N=444)**	**NGL 12.5 mg (N=441)**	**NGL 25 mg (N=446)**	**Usual Care (N=270)**	**NGL 25 mg (N=534)**
Any AE	227 (51.1)	231 (52.4)	283 (63.5)	194 (71.9)	428 (80.1)
Any SAE (including events with outcome=death)	20 (4.5)	20 (4.5)	14 (3.1)	30 (11.1)	46 (8.6)
Any DAE	21 (4.7)	20 (4.5)	46 (10.3)	NA[a]	50 (9.4)

[a] Patients randomized to Usual Care were treated with approved over-the-counter and/or prescription laxative(s) either as monotherapy or in any combination, according to the Investigator's clinical judgment. These patients were not taking investigational product and; therefore, could not discontinue investigational product.

Note: AEs that started on or after first dose through last dose of investigational product are included.

Note: AEs leading to discontinuation of investigational product only include those events that included permanent discontinuation of investigational product.

AE Adverse event; DAE Discontinuation of investigational product due to an AE; N Total number of patients; NA Not applicable; NGL Naloxegol.

3.5.2 Most common AEs

In the 12-week pooled data, differences between the treatment groups in the AE rate were primarily related to GI AE incidences (Table 7). This was expected based on the mechanism of action in which naloxegol binds to μ-opioid receptors at plexi in the enteric nervous system leading to reversal of opioid agonist-induced GI pharmacodynamic effects.

Most AEs were mild to moderate in intensity.

The prevalence (ie, proportion of patients reporting an AE on a given day) of the most common GI AEs decreased over the course of treatment (Figure 8). The prevalence of diarrhea, nausea, and vomiting in both naloxegol dose groups decreased to levels comparable to placebo, whereas the prevalence of abdominal pain, flatulence, and upper abdominal pain in both naloxegol dose groups remained higher than in the placebo group during the treatment period. Similar frequency and pattern of GI events for naloxegol 25 mg were observed in the controlled 52-week long-term safety study (Appendix Table 23).

Among the non-GI AEs with an incidence ≥2% in any treatment group, there were more patients with back pain and pain in extremity events in the naloxegol 25 mg group than in the naloxegol 12.5 mg and placebo groups in Studies K4 and K5 (4.3% versus 2.7% and 2.0%, respectively, for back pain and 2.2% versus 1.1% and 0.7%, respectively, for pain in extremity). There were also more patients reporting the AE of hyperhidrosis in the naloxegol 25 mg group than in the naloxegol 12.5 mg and placebo groups (2.9% in the naloxegol 25 mg group, 0.5% in the naloxegol 12.5 mg group, and 0.2% in the placebo group).

The number of clinically important events of back pain and pain in extremity was low. Of the reported back pain and pain in extremity AEs, the majority were reported as mild or moderate (15 of 19 back pain AEs and 7 of 10 pain in extremity AEs in the naloxegol 25 mg group; similar proportions of mild or moderate AEs were reported for the placebo and naloxegol 12.5 mg groups). There were no SAEs for back or extremity pain in the 12-week studies, and the number of DAEs was 1 for placebo for 'back pain,' 2 for naloxegol 25 mg for 'back pain,' and 1 for naloxegol 25 mg for 'extremity pain.' Among patients with an AE of either back pain or pain in extremity during the treatment period (12 patients on placebo [2.7%], 17 patients on naloxegol 12.5 mg [3.9%], and 24 patients on naloxegol 25 mg [5.4%]), Numeric Rating Scale (NRS) and opioid use remained stable, and coincident increases in weekly NRS of ≥2 (2 of 12 on placebo, 1 of 17 on naloxegol 12.5 mg, and 4 of 24 on naloxegol 25 mg) or in opioid use of ≥30% (3 of 12 on placebo, 0 of 17 on naloxegol 12.5 mg, and 4 of 24 on naloxegol 25 mg) over 12 weeks were infrequent and similar across treatment groups.

These differences in AEs of back pain and pain in extremity were not replicated in the long-term safety study (Study K8). In that study, the frequency of AE reports of back pain was 9.0% for naloxegol 25 mg versus 8.9% for Usual Care. For extremity pain, the rate for naloxegol 25 mg was 3.7% versus 3.0% for Usual Care.

None of the hyperhidrosis events were reported as an SAE. Four of the 13 events of hyperhidrosis in the naloxegol 25 mg group led to discontinuation. Eleven of the 13 events in the naloxegol 25 mg group were reported as mild or moderate. Seven of the 13 patients in the naloxegol 25 mg group who reported hyperhidrosis also reported concurrent GI AEs.

This difference was also seen in the 52-week study, in which 3.2% of patients in the naloxegol 25 mg group reported hyperhidrosis as compared to 0.4% in the Usual Care group.

Table 7 Number (%) of patients with the most common (≥2% incidence in any treatment group) AEs during the treatment period (12-week pool [Studies K4 and K5])

Preferred term	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)
Patients with any AE	227 (51.1)	231 (52.4)	283 (63.5)
Abdominal pain	25 (5.6)	43 (9.8)	71 (15.9)
Diarrhea	19 (4.3)	25 (5.7)	41 (9.2)
Nausea	20 (4.5)	29 (6.6)	36 (8.1)
Flatulence	11 (2.5)	13 (2.9)	26 (5.8)
Headache	12 (2.7)	17 (3.9)	20 (4.5)
Vomiting	13 (2.9)	10 (2.3)	20 (4.5)
Back pain	9 (2.0)	12 (2.7)	19 (4.3)
Abdominal pain upper	7 (1.6)	8 (1.8)	17 (3.8)
Hyperhidrosis	1 (0.2)	2 (0.5)	13 (2.9)
Abdominal distension	9 (2.0)	11 (2.5)	11 (2.5)
Upper respiratory tract infection	12 (2.7)	9 (2.0)	11 (2.5)
Fatigue	6 (1.4)	7 (1.6)	10 (2.2)
Sinusitis	6 (1.4)	6 (1.4)	10 (2.2)
Pain in extremity	3 (0.7)	5 (1.1)	10 (2.2)
Nasopharyngitis	1 (0.2)	5 (1.1)	9 (2.0)
Fall	8 (1.8)	9 (2.0)	4 (0.9)
Dizziness	9 (2.0)	11 (2.5)	3 (0.7)

Note: Patients with events in ≥1 PT are counted once in each of those PTs. AEs that started on or after the first dose through the last dose of investigational product are included. AEs are sorted by PT in decreasing order of frequency (by total number on naloxegol 25 mg, naloxegol 12.5 mg, then placebo).

AE Adverse event; N Total number of patients; NGL Naloxegol; PT Preferred term.

3.6 Recommended proposed dosing

The naloxegol 25 mg dose is recommended as the starting dose for most patients based on replicated efficacy for the primary end point in both pivotal trials. Although the 12.5 mg dose did not demonstrate replicated statistically significant improvements on the primary efficacy endpoint, results of secondary endpoints in both studies support that the dose is biologically active and, as such, it may offer benefit to some patients. The overall tolerability of the 12.5 mg dose based on common AEs, discontinuations due to AEs, and the incidence of Investigator-reported OWD AEs was numerically closer to the placebo group.

AstraZeneca's current position with regard to the 12.5 mg dose is that it may be used as a starting dose in some subpopulations.

In addition, consideration may be given to lowering the dose to 12.5 mg in patients experiencing severe GI AEs depending upon the response and tolerability of individual patients.

4. OPIOID ANTAGONISTS AND CARDIOVASCULAR SAFETY

A summary of the findings in the literature on topics related to chronic opioid antagonists and cardiovascular (CV) effects together with relevant information from product labels is provided in Section 4.1. Sections 4.2 and 4.3 provide CV evaluation of naloxegol data.

4.1 CV experience with chronic opioid antagonists

A literature search did not reveal a clear consensus on potential adverse effects of peripherally acting opioid antagonists on CV parameters. CV parameters have been evaluated following treatment with peripheral opioid antagonists (Holzer 2012, Anissian et al 2012, Becker and Blum 2009, Greenwald et al 2003, Guay 2009). Anissian et al 2012 and review articles (Greenwald et al 2003, Guay 2009) noted a higher incidence of hypotension with methylnaltrexone versus placebo, while 1 study noted a lower incidence of both hypotension and tachycardia with methylnaltrexone versus placebo (Thomas et al 2008). Higher rates of myocardial infarction (MI) versus placebo is reported from the 12-month study of alvimopan (Becker and Blum 2009, Bream-Rouwenhorst and Cantrell 2009; ie, Study GSK-014), while a matched-cohort study of alvimopan (Delaney et al 2012) noted lower rates of CV morbidity with alvimopan versus placebo.

Extensive clinical and post-marketing experience is available with a marketed oral, once-a-day, μ-opioid-receptor antagonist for chronic use, naltrexone, for indications other than opioid-induced constipation. Naltrexone (including REVIA®, VIVITROL®, and others) is indicated for the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. Unlike naloxegol, naltrexone is not excluded from the central nervous system (CNS).

- REVIA, administered as daily tablets, was first approved in the United States (US) in 1984 for opioid dependence and for treatment of alcohol dependence in 1994 (REVIA Prescribing Information 2013).
- VIVITROL, administered as an extended-release injectable suspension, was first approved in 2006 for alcohol dependence, and in 2010 for opioid dependence (VIVITROL Prescribing Information 2010).

CV effects with naltrexone are rare and comparable to placebo. The Cochran review (Rösner et al 2010) on opioid antagonists for alcohol dependence lists a total of 50 randomized clinical trials (47 on naltrexone and 3 on nalfemene) in 7793 patients. In Rösner et al (Rösner et al 2010), SAEs were reported from 9 of those studies, which included a total of 1526 patients, of whom 869 were on naltrexone and 657 were on placebo (see Table 1.46 in Rösner et al 2010). In Kranzler (Kranzler et al 2004), 1 patient (0.6%) on naltrexone reported chest pain versus

7 patients on placebo (4.2%). In 1 study (Morris et al 2001), 1 patient (2.6%) on naltrexone reported atypical chest pain and thrombophlebitis, although not reported as potentially related to treatment. In Petrakis (Petrakis et al 2005), 2 patients (3.0%) in the disulfiram and naltrexone group had cardiac events requiring hospitalization, compared to 1 (1.5%) in the disulfiram and placebo group. No events were reported from the naltrexone only and placebo only groups. No other of the 9 studies in Table 1.46 in Rösner et al (Rösner et al 2010) reported any CV AE in the publication. In the 3 largest studies included in the meta-analysis there were no CV AE reported in the respective publications: Anton (Anton et al 2006) 614 randomized to naltrexone w/wo background treatment versus 769 on comparator; Krystal (Krystal et al 2001) with 418 on naltrexone versus 209 on placebo; and Garbutt (Garbutt et al 2005) with 415 on naltrexone versus 209 on placebo.

In the 2006 FDA review of VIVITROL in alcohol-dependent patients, the incidence of CV SAEs with VIVITROL was low and similar to placebo in studies 4 to 6 months of duration (Table 7.1.2.2.3, VIVITROL FDA Reviewers' Analysis 2006) based on 780 patients on VIVITROL versus 214 on placebo. Three events (MI, chest tightness, and atrial fibrillation) were reported on VIVITROL versus 1 (atrial fibrillation) on placebo.

The use of naltrexone in opioid dependent patients is covered in the Cochran review by Minozzi (Minozzi et al 2011) including 13 randomized clinical trials in 1158 patients. However, SAEs were only reported from 4 studies (Table 1.6, Minozzi et al 2011), but with no specification of CV effects. In the supplemental New Drug Application material (ie, Study ALK21-013, part A) submitted in 2010 for VIVITROL in opioid-dependent patients, there were no CV SAEs reported either in VIVITROL (126 patients) or placebo (124 patients) (Table 15, VIVITROL Sponsor Briefing Document 2010). The number of reported AEs of hypertension were 6 (4.8%) on VIVITROL versus 4 (3.2%) on placebo (Table 13, VIVITROL Sponsor Briefing Document 2010).

Naloxone, as an intravenous medicine used for acute reversal of opioid CNS effects in urgent situations, is utilized in a population that is not representative of the population studied in the naloxegol clinical program.

4.2 CV evaluation of naloxegol in clinical pharmacology and nonclinical studies

The overall nonclinical CV safety assessment did not reveal any major effects on measured CV parameters at clinically relevant exposures. In addition, standard Phase I clinical safety studies up to a 1000 mg single dose and 500 mg/day repeated doses of naloxegol for up to 8 days showed no evidence of CV effects in healthy volunteers.

A battery of nonclinical tests supported the absence of any direct effects of naloxegol on the CV system. There were no effects on the human ether-à-go-go-related gene or any of the 7 cardiac ion channels tested (at concentrations of ≥815× the human maximum plasma drug concentration [C_{max}] after a 25 mg dose); no effects on contractility parameters in dog ventricular myocytes (at concentrations of ≥815× the human C_{max} after a 25 mg dose); and no effects on heart rate (HR), cardiac contractility parameters, or coronary flow in isolated rat hearts (at concentrations of ≥81× the human C_{max} after a 25 mg dose). In a single-dose dog telemetry study, no CV effects were noted at exposures similar to those achieved in the clinical studies at the 25 mg dose. A decrease in arterial BP, left ventricular systolic pressure, and indices of cardiac contractility and an increase in HR were noted at exposures ≥6.7× higher than those achieved in the clinical studies at the 25 mg dose. In repeat-dose toxicity studies in the dog (up to 9 months; at least 66× higher than human C_{max} at the proposed 25 mg dose), no effects were seen on electrophysiological or hemodynamic CV parameters. The hemodynamic changes seen in the single-dose dog telemetry study were not seen in the clinical studies (for clinical details, see Section 4.3).

The results of the clinical pharmacology studies in more than 400 patients, vital signs, oral temperature, oxygen saturation, 12-lead electrocardiogram (ECG), cardiac limb lead monitoring, and clinical laboratory results did not raise any safety concerns. An overview of BP changes across the Phase I studies has shown that these changes were generally similar between naloxegol-treated and placebo-treated patients. The AEs of decreased BP, orthostatic hypotension, and dizziness in naloxegol-treated patients were transient and resolved spontaneously; none was serious or led to discontinuation of investigational product; and all, except for 1 case of orthostatic hypotension following a 25 mg dose of naloxegol, occurred at naloxegol dose levels of 50 mg or higher. The thorough QT study, using naloxegol 25 mg (therapeutic dose) and naloxegol 150 mg (supratherapeutic dose) compared with placebo, using moxifloxacin as a positive control, showed that naloxegol did not prolong the placebo-corrected, baseline-adjusted, Fridericia QT interval; the upper bound of the 2-sided 90% confidence intervals (CI) was below 10 ms at all time points post-dose.

4.3 CV evaluation in the naloxegol Phase III studies

AstraZeneca reviewed the clinical data collected for up to 52 weeks, including prespecified CV analyses, prospective independent adjudication of major adverse cardiovascular events (MACE), and additional post hoc analyses.

CV events were defined as a topic of special interest in the Phase III program because of findings in a dog telemetry study (ie, decreased BP and heart contractility) and because of a potential CV safety signal (myocardial ischemia) reported from a single long-term safety study of alvimopan in patients with opioid bowel dysfunction (Study GSK-014). Additional safety assessments were included to better understand the risk for CV AEs, mitigate risk, and enhance patient safety, including a 4-hour observation period after the first dose of investigational product, with data collection at approximately the time of C_{max} (1-hour post-first-dose vital signs measurements, and 2-hour post-first-dose ECG). In addition, ECGs were centrally read by an ECG cardiology service provider blinded to the investigational product received. Results from vital signs measurements and AEs related to BP are presented in detail in Sections 4.3.5 and 4.3.6, respectively. In the pivotal studies, sparse pharmacokinetic (PK) sampling was conducted on Day 1 (2 hours after the first dose of study drug), and at scheduled visits thereafter.

In the Phase II study, the proportion of patients with AEs in the cardiac disorders System Organ Class was similar among the treatment groups (placebo and naloxegol 5, 25, and

50 mg). No relevant differences in mean vital sign values were noted between naloxegol and placebo, and no trends in change from baseline values over time were detected. There were no clinically relevant ECG findings in patients who received naloxegol.

4.3.1 CV Event Adjudication Committee

In the naloxegol Phase III program, AstraZeneca prospectively organized an independent, external Cardiovascular Event Adjudication Committee (CV-EAC). CV-EAC members were experienced in neurovascular and CV medicine and clinical study event adjudication, remained blinded to randomization, and completed their assessments prior to database lock.

All CV-type SAEs and selected non-serious CV-type AEs were sent for adjudication. Predefined CV adjudication outcomes included “MACE” (CV death, MI, and stroke) as well as CV events leading to hospitalization for heart failure or unstable angina. By adjudication charter, unexplained deaths were to be adjudicated as CV deaths.

4.3.2 MACE

A total of 68 unique events of CV SAEs and potentially relevant CV AEs (23 AEs in 18 of 700 patients who received placebo or Usual Care and 45 AEs in 36 of 1386 patients who received naloxegol) for 54 unique patients were submitted to the CV-EAC for adjudication. Of these, 10 events in 9 patients were adjudicated as MACE. A summary of patients with ≥1 CV outcome event during the treatment period or post-treatment follow-up as determined by the independent CV-EAC is presented in Table 8. The overall incidence of adjudicated MACE was low and similar across treatment groups both in the placebo-controlled studies and in the randomized, long-term safety study.

Table 8 Number (%) of patients with ≥1 CV outcome event during the treatment period or post-treatment follow-up as determined by the independent CV-EAC (placebo-controlled pool and Study K8)

	Placebo-controlled pool (Studies K4/K7 and K5)			52-week safety study (Study K8)	
Category	**Placebo (N=444)**	**NGL 12.5 mg (N=441)**	**NGL 25 mg (N=446)**	**Usual Care (N=270)**	**NGL 25 mg (N=534)**
Any MACE per CV-EAC	**2 (0.5)**	**2 (0.5)**	**1 (0.2)**	**2 (0.7)**	**2 (0.4)**
CV death	0	2 (0.5)	0	1 (0.4)	1 (0.2)
Acute MI	2 (0.5)	1 (0.2)[a]	1 (0.2)[b]	0	1 (0.2)
Stroke	0	0	0	1 (0.4)	0
Events per 100 PY	**1.5**	**1.6**	**0.8**	**0.9**	**0.5**
Other CV events of interest per CV-EAC					
Hospitalization for unstable angina	0	0	0	0	0
Hospitalization for heart failure	0	0	1 (0.2)	1 (0.4)	0

a Patient had an acute MI and later had an event adjudicated as CV death.

b Naloxegol 25 mg: a 40- to 44-year-old male with a medical history of multiple CV risk factors had a severe MI on Day 1, and investigational product was discontinued. The MI was reported as resolved on Day 3. The CV-EAC asked for additional information regarding this patient and received the following information from the study site: The patient died approximately 16 months after the MI, presumably due to aortic dissection, hypoxic respiratory failure, and renal failure. This death is not captured in the clinical database and is therefore not included in either Study K4 or pooled data presentations.

CV Cardiovascular; CV-EAC Cardiovascular Event Adjudication Committee; MACE Major adverse cardiovascular event; MI Myocardial infarction; N Total number of patients; NGL Naloxegol; PY Patient-years.

Rates per 100 patient-years of exposure were calculated. Because of the low number of events, and the absence of an increased rate in the naloxegol 25 mg as compared to naloxegol 12.5 mg, the naloxegol doses were combined and compared against placebo/Usual Care to characterize results in the entire Phase III program. Presentations of the CIs around the estimated event rates and associated relative risk were conducted post hoc. Because of the small number of events, exact intervals were preferred, which were estimated in PROC StatXact based on the Poisson distribution. Corresponding exact CIs for the absolute risk difference are not available in this software but were estimated via the Cochran-Mantel-Haenszel approach, with asymptotic 95% CIs.

The incidence of MACE adjudicated by the CV-EAC as meeting formal diagnostic criteria was 0.6% (4/700 patients) for placebo or Usual Care versus 0.4% (5/1386 patients) for naloxegol (Table 9). The MACE rate per 100 patient-years of exposure was 1.13 (95% CI 0.31, 2.89) for placebo or Usual Care versus 0.75 (95% CI 0.24, 1.75) for naloxegol, with a relative risk (naloxegol versus placebo or Usual Care) of 0.66 (95% CI 0.14, 3.34). Similarly, the incidence of MI adjudicated by the CV-EAC as meeting formal diagnostic criteria was

0.3% for placebo or Usual Care versus 0.2% for naloxegol. The MI rate per 100 patient-years of exposure was 0.56 (95% CI 0.07, 2.04) for placebo or Usual Care versus 0.45 (95% CI 0.09, 1.32) for naloxegol, with a relative risk (naloxegol versus placebo or Usual Care) of 0.79 (95% CI 0.09, 9.41).

Key information for each of the 9 patients adjudicated with MACE and for 2 patients adjudicated with hospitalization due to heart failure are provided in Appendix Table 30.

Table 9 Estimated event rates for adjudicated MACE and MI in the naloxegol Phase III program (placebo-controlled pool and Study K8)

Event	Placebo/ Usual Care (N=700)[a] (354.9 PY)[b]	Naloxegol 12.5 mg/25 mg (N=1386)[a] (665.9 PY)[b]	Naloxegol 12.5 mg/25 mg versus placebo/Usual Care: Relative risk[c]	Naloxegol 12.5 mg/25 mg versus placebo/Usual Care: Risk difference[d]
MACE (CV death, MI, and stroke)				
n (%)[e]	4 (0.6%)	5 (0.4%)		
Rate (95% CI)[f]	1.13 (0.31, 2.89)	0.75 (0.24, 1.75)	0.66 (0.14, 3.34)	-0.38 (-1.67, 0.91)
MI				
n (%)[e]	2 (0.3%)	3 (0.2%)		
Rate (95% CI)[f]	0.56 (0.07, 2.04)	0.45 (0.09, 1.32)	0.79 (0.09, 9.41)	-0.12 (-1.06, 0.82)

[a] Unique number of patients who received at least 1 dose of study medication in each treatment group.
[b] Total patient-years of on-study follow-up.
[c] Estimates and exact 95% CI based on the Poisson distribution stratified by study.
[d] Mantel-Haenszel estimates (per 100 PY) and 95% CI stratified by study.
[e] Unique number of patients with event in each treatment group.
[f] Crude event rates (per 100 PY) and exact 95% CI based on the Poisson distribution.
CI Confidence interval; CV Cardiovascular; MACE Major adverse cardiovascular event; MI Myocardial infarction; N Total number of patients; n Number of patients with event; PY Patient-years.

To the knowledge of AstraZeneca, there are no published observational study data available for describing risk of CV events within a patient population suffering from OIC. As a result, patients chronically exposed to opioids were used to characterize a background CV event rate. These comprised a retrospective, claims-based study (Carman et al 2011) that analyzed the incidence of MI using a large, administrative US-claims database of privately insured patients taking opioids for >180 days and another observational study that used a different, large, geographically diverse US administrative claims database (LoCasale 2013). The retrospective study found that patients taking opioids for >180 days differ substantially from those taking opioids <10 days and from those not taking opioids (Carman et al 2011).

The MI rates per 100 patient-years of exposure seen in the naloxegol treatment groups (0.45, 95% CI: 0.09, 1.32) are within the range of background event rates for MI among chronic opioid users without a history of MI (ie, excluding patients with an MI within the past 6 months, Carman et al 2011; and excluding patients with an MI within the past 18 months, LoCasale 2013), in which MI rates per 100 patient-years of exposure were 0.60 (95% CI: 0.57, 0.64) and 0.83 (95% CI: 0.69, 1.00), respectively (Table 10).

Table 10 MI event rates in observational studies in patients treated with opioid chronically without a history of MI

	Carman et al 2011 (N=148657, 176732 PY)		LoCasale 2013 (N=16893, 13803.2 PY)	
CV event	**Patients with event (n [%])**	**Event rate (CI)[a]**	**Patients with event (n [%])**	**Event rate (CI)[a]**
Myocardial infarction	1067 (0.7%)	0.60 (0.57, 0.64)	115 (0.7%)	0.83 (0.69, 1.00)

[a] CIs are exact 95% CIs based on the Poisson distribution. Event rates are calculated as the number of patients having at least 1 event divided by the total number of person-years of observation × 100 (as per 100 patient-years), where observation ends at the time of first event or end of follow-up.

CI Confidence interval (95%); CV Cardiovascular; MI Myocardial infarction; N Number of patients; n number of patients with event; PY patient-years.

4.3.3 CV SAEs

The incidence of SAEs of cardiac disorders was 0.6% (8/1386) for naloxegol and 1.1% (8/700) for comparator (placebo and Usual Care) in the Phase III program. The incidence of vascular disorder SAEs was 0.6% (8/1386) for naloxegol and 0.1% (1/700) for comparator (placebo and Usual Care), and the difference was a result of several reports across multiple preferred terms (Table 11).

Table 11 Number (%) of patients who had ≥1 CV SAE by SOC and preferred terms during the treatment period or post-treatment follow-up (Studies K4, K5, K7, and K8)

	Placebo-controlled pool (Studies K4/K7 and K5)			52-week safety study (Study K8)	
SOC **Preferred terms**	**Placebo (N=444)**	**Naloxegol 12.5 mg (N=441)**	**Naloxegol 25 mg (N=446)**	**Usual Care (N=270)**	**Naloxegol 25 mg (N=534)**
Any CV SAE	5 (1.1%)	5 (1.1%)	5 (1.1%)	4 (1.5%)	5 (0.9%)
Cardiac Disorders	5 (1.1%)	3 (0.7%)	3 (0.7%)	3 (1.1%)	2 (0.4%)
Coronary artery disease	1	0	1	0	0
Cardiac failure congestive	0	0	1	1	0
Myocardial infarction	0	0	1	0	0
Acute myocardial infarction	1	1	0	0	0
Atrial flutter	0	1	0	0	0
Myocardial ischemia	0	1	0	1	0
Angina pectoris	1	0	0	0	0
Palpitations	1	0	0	0	0
Angina unstable	1	0	0	0	0
Atrial fibrillation	0	0	0	1	2
Vascular Disorders	0	2 (0.5%)	3 (0.7%)	1 (0.4%)	3 (0.6%)
Accelerated hypertension	0	0	1	0	0
Malignant hypertension	0	0	1	0	0
Hypotension	0	1	1	0	0
Hypertension	0	1	0	0	0
Deep vein thrombosis	0	0	0	0	1
Hypovolaemic shock	0	0	0	0	1
Orthostatic hypotension	0	0	0	0	1
Thrombosis	0	0	0	1	0

Note: Patients are counted once per SOC and PT.
CV Cardiovascular; N Total number of patients; PT Preferred term; SAE Serious adverse event; SOC System Organ Class.

The majority of the CV SAEs occurred among patients categorized in the risk group with CV disease, diabetes, or ≥2 risk factors at baseline (Table 12). Notably, the incidence of CV SAEs in each of the CV risk category groups ranged from 0% to 3.7% and was similar across the treatment groups.

Table 12 Number of patients who had ≥1 CV SAE during the treatment period, by baseline CV risk classes (Studies K4, K5, K7, and K8)

		Placebo-controlled pool (Studies K4/K7 and K5)			52-week safety study (Study K8)	
Category		**Placebo**	**NGL 12.5 mg**	**NGL 25 mg**	**Usual Care**	**NGL 25 mg**
All patients	N	444	441	446	270	534
	Any CV SAE	5 (1.1%)	5 (1.1%)	5 (1.1%)	4 (1.5%)	5 (0.9%)
Patients (%) in CV risk classes[a]						
Diabetes, history of CV disease, or ≥2 other risk factors	N	177	177	198	108	214
	Any CV SAE	5 (2.8%)	4 (2.3%)	5 (2.5%)	4 (3.7%)	4 (1.9%)
One risk factor (excluding diabetes and history of CV disease)	N	130	116	110	81	145
	Any CV SAE	0	1 (0.9%)	0	0	1 (0.7%)
No risk factor	N	137	148	138	81	175
	Any CV SAE	0	0	0	0	0

[a] Post hoc classification of CV risk at baseline (White et al 2002, Wilson et al 1998) based on the following risk factors: age >75 years, hypertension or on hypertensive medication, hyperlipidemia or use of lipid-lowering medication, current smoker, use of low-dose aspirin for a CV-related indication, diabetes, and prior history of CV disease.

Note: Percentages are based on the total number of patients in each patient and treatment group.

Note: Any CV SAE with MedDRA System Organ Class Name (AEBODSYS) as "CARDIAC DISORDERS" or "VASCULAR DISORDERS".

CV Cardiovascular; N Total number of patients; NGL Naloxegol; MedDRA Medical Dictionary for Regulatory Activities; SAE Serious adverse event.

In addition, cerebrovascular SAEs were reported in 5 patients (2 among 700 patients on placebo or Usual Care and 3 among 1386 patients on naloxegol [1 on 12.5 mg and 2 on 25 mg]). The 2 SAEs on placebo/Usual Care were cerebrovascular accident and ischemic cerebral infarction (both reported in the Usual Care group in Study K8). The 3 SAEs on naloxegol were subdural hemorrhage, aphasia, and transient ischemic attack, all of which were reported in the placebo-controlled pool. One of these 5 cerebrovascular SAEs was adjudicated as MACE (ischemic cerebral infarction in the Usual Care group was adjudicated as stroke). Four (2 on naloxegol 25 mg and 2 on Usual Care) of the 5 patients with cerebrovascular SAEs had diabetes, history of CV disease, or ≥2 other risk factors, and the other patient (on naloxegol 12.5 mg) had 1 risk factor.

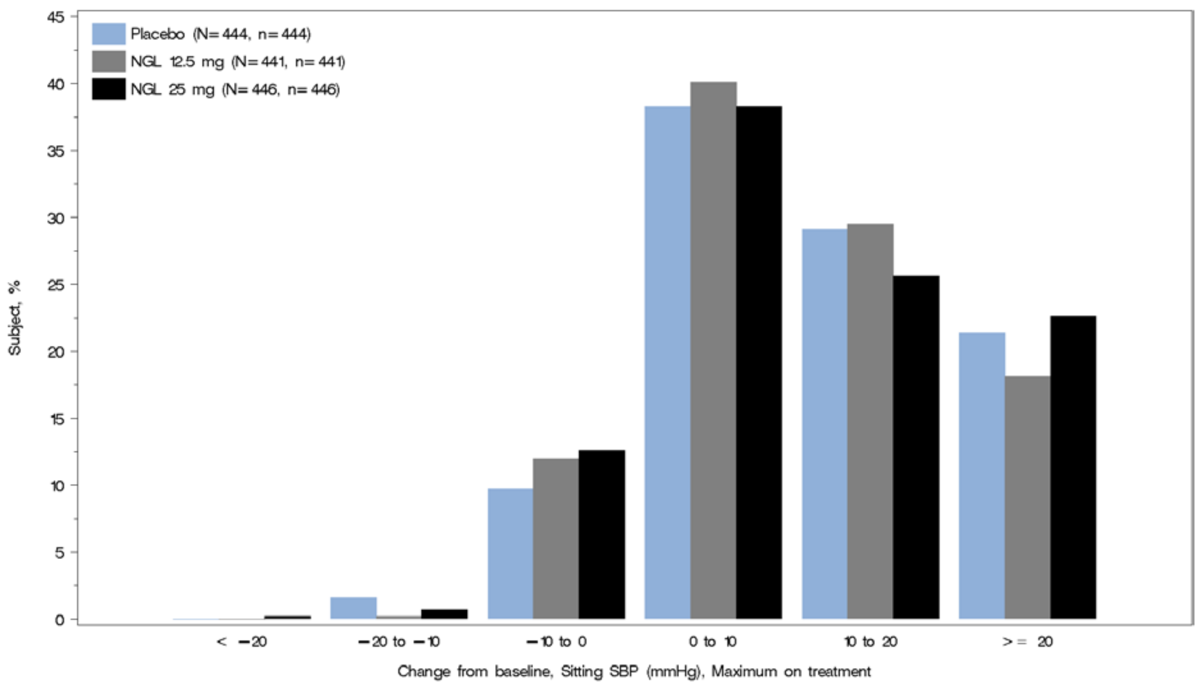
4.3.4 ECGs

ECGs were assessed at baseline, before and after first dose, 2 hours post-dose near the time of C_{max}, and at all study visits. ECGs were centrally read by an ECG cardiology service provider blinded to the investigational product received and assessed as normal or abnormal. Mean changes from baseline and the proportion of patients with ECG parameter values outside of prespecified reference ranges were similar across the treatment groups.

4.3.5 Hemodynamic changes

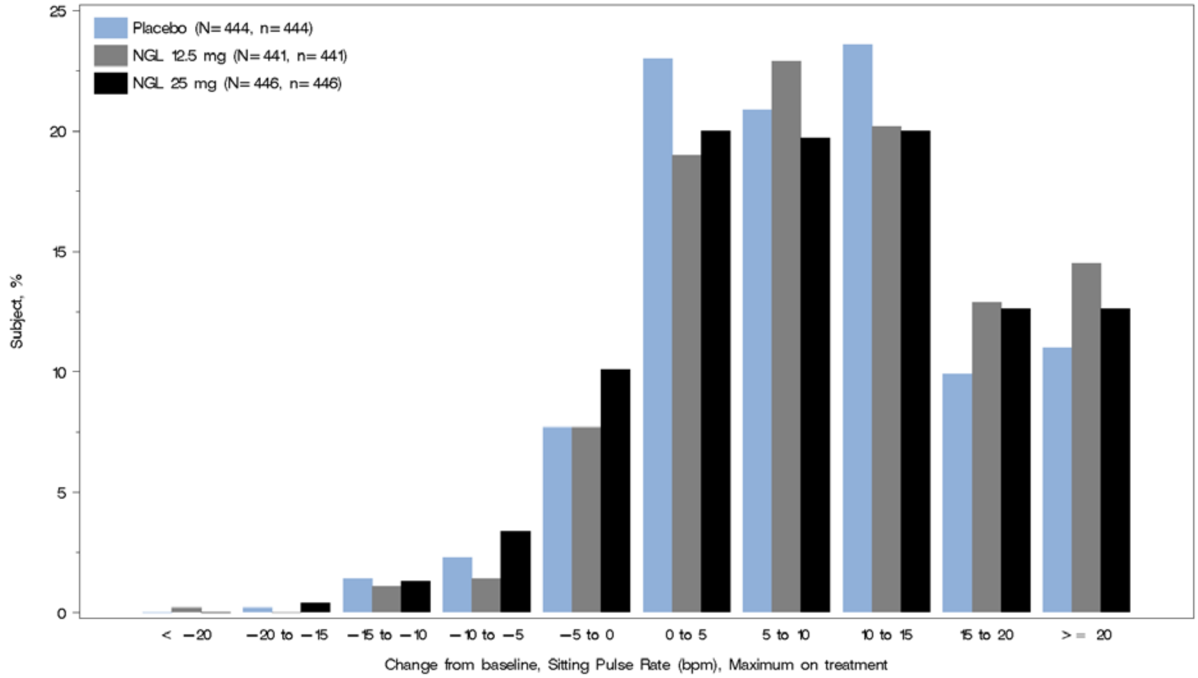
In the naloxegol Phase III program, vital signs were collected at every visit, including after the first dose, when patients were kept for a 4-hour observation period to coincide with the time of C_{max}. Mean changes from baseline in vital signs (Appendix Table 32) considering both the 1-hour post-first-dose assessment and assessments at any time during the study, and the pattern or frequency of vital signs outliers based on maximum on-treatment values (Figure 3 and Figure 4) and on values 1 hour after the first dose (Figure 11 and Figure 12), were similar across the treatment groups for both naloxegol 12.5 mg and 25 mg.

Figure 3 Change from baseline in sitting systolic blood pressure (mmHg), maximum on treatment (Studies K4 and K5)



Categories include the lower limit of the interval (eg, 0 to 10 means >= 0 to < 10). The denominator for the percentages is the number of patients (n) with both a non−missing baseline value and a non−missing value at respective assessment.

Figure 4 **Change from baseline in sitting pulse (bpm), maximum on treatment (Studies K4 and K5)**



Categories include the lower limit of the interval (eg, 0 to 10 means >= 0 to < 10). The denominator for the percentages is the number of patients (n) with both a non−missing baseline value and a non−missing value at respective assessment.

To collect exposure (C_{max} and area under the plasma concentration time curve from 0 to infinity [$AUC_{0-\infty}$]) data, sparse sampling was used in Studies K4 and K5. For patients whose PK samples were available, there is no evidence to suggest a correlation between naloxegol steady-state AUC (observed or predicted from population PK modelling) and observed vital signs and pulse values.

Another parameter to assess the stress and energy demand of the heart is the rate-pressure product, which is based on the number of times the heart needs to beat per minute (pulse rate) and the arterial BP that it is pumping against (systolic blood pressure [SBP]). Table 13 shows the values and changes from baseline in rate-pressure product in the 12-week studies and the long-term safety study. Rate-pressure product changes from baseline were similar across treatment groups.

Table 13 Change from baseline in rate-pressure product during the treatment period (12-week pool and Study K8)

	12-week pool (Studies K4 and K5)			52-week safety study (Study K8)	
	Placebo (N=444)	**NGL 12.5 mg (N=441)**	**NGL 25 mg (N=446)**	**Usual Care (N=270)**	**NGL 25 mg (N=534)**
Mean (SD) baseline[a]					
Baseline	8853.60 (1628.30)	9085.50 (1753.39)	8933.70 (1835.11)	8861.3 (1735.05)	8984.8 (1779.26)
Mean (SD) change from baseline[a]					
Day 1, 1-hour post-dose	-235.50 (1021.14)	-235.60 (1102.14)	-176.9 (1245.58)	-84.3 (1344.04)	-134.7 (1305.33)
Last on treatment	228.40 (1582.75)	259.7 (1607.70)	210.4 (1760.47)	232.0 (1843.41)	298.1 (1790.58)

[a] The formula for the rate-pressure product is rate-pressure product=SBP (mmHg) × pulse rate (bpm).
N Total number of patients; NGL Naloxegol; SBP systolic blood pressure; SD Standard deviation.

4.3.6 AEs related to blood pressure

In addition to evaluating changes in measured vital signs, AstraZeneca also evaluated AEs related to changes in BP, categorized as decreased BP, syncope, and increased BP (Table 14).

The incidence of decreased BP AEs was similar across the treatment groups, ranging from 0.5% for naloxegol 12.5 mg to 1.9% in the Usual Care group.

Table 14 Number (%) of patients with ≥1 AE related to BP changes during the treatment period (12-week pool and Study K8)

	Placebo-controlled pool (Studies K4 and K5)			52-week safety study (Study K8)	
Topic **Preferred term**	**Placebo (N=444)**	**NGL 12.5 mg (N=441)**	**NGL 25 mg (N=446)**	**Usual Care (N=270)**	**NGL 25 mg (N=534)**
Decreased BP	**3 (0.7)**	**2 (0.5)**	**6 (1.3)**	**5 (1.9)**	**5 (0.9)**
Hypotension	1 (0.2)	2 (0.5)	3 (0.7)	1 (0.4)	1 (0.2)
BP decreased	2 (0.5)	0	2 (0.4)	3 (1.1)	3 (0.6)
Orthostatic hypotension	0	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)
Syncope	**0**	**2 (0.5)**	**1 (0.2)**	**0**	**3 (0.6)**
Syncope	0	2 (0.5)	1 (0.2)	0	3 (0.6)
Increased BP	**5 (1.1)**	**10 (2.3)**	**13 (2.9)**	**12 (4.4)**	**21 (3.9)**
Hypertension	3 (0.7)	6 (1.4)	8 (1.8)	9 (3.3)	13 (2.4)
BP increased	2 (0.5)	4 (0.9)	3 (0.7)	3 (1.1)	7 (1.3)
Accelerated hypertension	0	0	1 (0.2)	0	0
Malignant hypertension	0	0	1 (0.2)	0	0
BP diastolic increased	0	0	0	0	1 (0.2)

AE Adverse event; BP Blood pressure; N Total number of patients; NGL Naloxegol.

In the Phase III studies, syncope was reported for 6 of 1386 patients in the naloxegol groups (2 on 12.5 mg and 4 on 25 mg) and none of the 700 patients in the comparator groups (placebo or Usual Care). There was no temporal pattern observed, and these 6 patients had contributing concomitant medication and/or relevant medical history. Three of the 6 were SAEs. None of these 6 patients with syncope AEs had an Investigator-reported OWD event (Section 7.1). Additional detail on these 6 patients is provided in Appendix Table 31.

In the 12-week pool, the proportion of patients with increased BP AEs was 1.1% in the placebo group, 2.3% in the naloxegol 12.5 mg group, and 2.9% in the naloxegol 25 mg group. The incidence of increased BP AEs was similar between the naloxegol 25 mg (3.9%) and Usual Care (4.4%) groups in the long-term safety study (Study K8). The majority (approximately 65%) of the patients with these AEs of increased BP had either a history of hypertension or elevated BP at baseline. In the 12-week pool, 1 of the 10 events on 12.5 mg and 2 of the 13 events on 25 mg were SAEs, and 1 patient on placebo was discontinued from investigational product due to an AE. None of the patients who had AEs of increased BP had an Investigator-reported OWD event (Section 7.1). A brief description of the SAEs of accelerated hypertension and malignant hypertension is provided here:

The SAE of "accelerated hypertension" occurred in a 65- to 69-year-old woman with baseline BP of 185/96 mmHg. She had not been taking her antihypertensive medication, nisoldipine. Her pressure rose to 231/103 mmHg on the first day of dosing. She had no symptoms and recovered without sequelae.

The SAE of "malignant hypertension" occurred in a 55- to 59-year-old woman with baseline BP of 169/82 mmHg. Anti-hypertensive medication compliance was not reported. On Day 85, she saw her primary physician because of headache; she was admitted to the hospital with a BP of 193/78 mmHg but had no other CNS symptoms. Her BP resolved 2 days later, and she was discharged.

4.3.7 Blood pressure assessment based on established external criteria

Based on the higher incidence of BP AEs seen on naloxegol in the 12-week pool, but not in the long-term safety study, a post hoc analysis was conducted in all patients, and in the cohort of patients with baseline hypertension, to better understand the potential for increases in BP with naloxegol treatment. These additional SBP (≥140 mmHg on 2 or more occasions) and diastolic BP (≥90 mmHg on 2 or more occasions) criteria were consistent with the established criteria for hypertension as outlined in "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 2004).

Table 15 displays JNC criteria (JNC 2004) for hypertension during treatment in the clinical program for all patients and patients with baseline hypertension. These data show no increased occurrence of hypertension during treatment with naloxegol compared to placebo or Usual Care, including in patients with baseline hypertension.

Table 15 Hypertension (defined by JNC criteria) during treatment for all patients and those with a history of hypertension

	12-week pool (Studies K4 and K5)			52-week study (Study K8)	
Increased blood pressure criteria	**Placebo**	**Naloxegol 12.5 mg**	**Naloxegol 25 mg**	**Usual Care**	**Naloxegol 25 mg**
N	444	441	446	270	534
Patients with sitting SBP ≥140 mmHg, n (%)	82 (18.5)	71 (16.1)	65 (14.6)	66 (24.4)	92 (17.2)
Patients with sitting DBP ≥90 mmHg, n (%)	62 (14.0)	58 (13.2)	53 (11.9)	37 (13.7)	67 (12.5)
Patients with a history of hypertension at baseline					
N	221	204	237	142	257
Patients with sitting SBP ≥140 mmHg, n (%)	64 (29.0)	52 (25.5)	54 (22.8)	60 (42.3)	67 (26.1)
Patients with sitting DBP ≥90 mmHg, n (%)	45 (20.4)	39 (19.1)	35 (14.8)	32 (22.5)	49 (19.1)

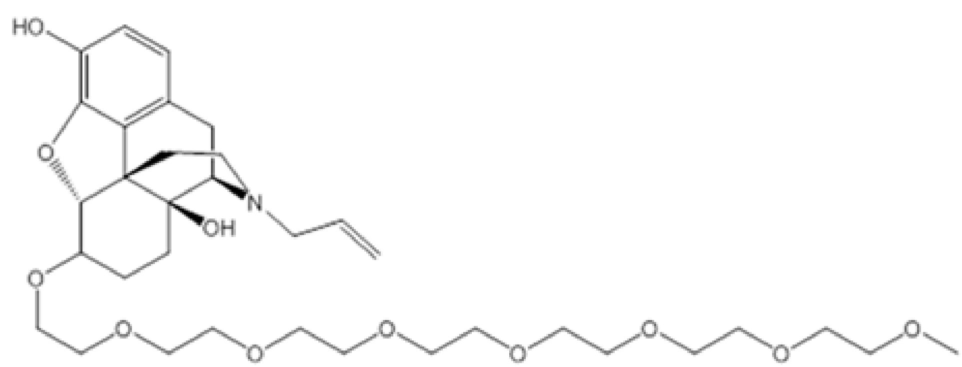
DBP Diastolic blood pressure; JNC Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; N The number of patients in each cohort (all patients or patients with a history of hypertension); n The number of patients with at least 2 measurements during treatment greater than or equal to the threshold value of 140 mmHg for SBP or 90 mmHg for DBP; SBP Systolic blood pressure.

5. PHARMACOLOGY OF NALOXEGOL

Naloxegol is a polyethylene glycol (PEG) derivative of naloxone designed to be excluded from the central nervous system (CNS). The low-molecular-weight PEG chain is covalently bound to the antagonist pharmacophore to create naloxegol, a new chemical entity (Figure 5). Pegylation confers 3 beneficial properties for naloxegol when compared to naloxone: (1) naloxegol has reduced passive permeability across membranes, (2) naloxegol is a P-glycoprotein (P-gp) efflux transporter substrate, and (3) naloxegol is orally bioavailable. The first 2 properties of naloxegol work together to reduce passive permeability/transport across the blood-brain barrier (BBB) and limit entry into the CNS compared to naloxone.

Naloxegol, by acting on the μ-opioid receptors in the periphery, was designed to directly and specifically address the causes of opioid-induced constipation (OIC; delayed transit time, increased fluid absorption, stimulated non-propulsive motility, reduced gastrointestinal [GI] secretions, and increased anal sphincter tone). Naloxegol is designed to alleviate OIC without reducing the central analgesic effects of opioids. This is supported by a lack of reversal of morphine-induced miosis (Section 5.3) and the lack of changes in Numeric Rating Scale scores while achieving efficacy (Section 6.6).

Figure 5 Chemical structure of naloxegol



Naloxegol

5.1 Naloxegol opioid receptor subtype binding and selectivity

The physiological effects of opioids are primarily mediated by 3 well-characterized opioid receptor subtypes, μ-, δ-, and κ-opioid receptors, which are distributed throughout the body. Based on literature evidence from in vitro and in vivo nonclinical studies, Table 16 provides an overview of opioid receptor expression and their main function.

Table 16 Overview of opioid receptor expression action

Opioid receptor type	μ-opioid receptors	κ-opioid receptors	δ-opioid receptors
Expression[a]	**GI system**: high **Brain**: high **Heart**: very low/absent	**GI system**: moderate **Brain**: high **Heart**: low	**GI system**: moderate **Brain**: high **Heart**: low
Relevant action of agonism[a]	Analgesia Euphoria Physical dependence Miosis Respiratory depression Reduced GI motility Possible vasodilation	Analgesia Miosis Sedation Inhibition of anti-diuretic hormone release Equivocal evidence for involvement in cardioprotection	Analgesia Euphoria Physical dependence Equivocal evidence for involvement in cardioprotection

[a] Based on in vitro cellular or in vivo animal data in Dragasis et al 2013, Hanna et al 2010, Headrick et al 2012, Wittert et al 1996, Sobanski et al 2014**.**

GI Gastrointestinal.

Naloxegol is a competitive antagonist of the μ- , κ-, and δ-opioid receptors with the highest affinity to μ- and κ-opioid receptors (K_i of 7.42 nM=4.8 ng/mL and 8.65 nM=5.6 ng/mL, respectively). Naloxegol has a 1.2-fold higher affinity at μ- than κ-opioid receptors, and 27-fold higher affinity at μ- than δ-opioid receptors (K_i of 203.0 nM=132 ng/mL)

The mean maximum plasma drug concentration (C_{max}) for naloxegol in the Phase II study (124 nM; 95% confidence interval of 87 nM to 162 nM) was above naloxegol's affinity for μ- and κ-opioid receptors. This is not the case for the δ-opioid receptor, indicating that naloxegol's ability to interfere with the agonism of the δ-opioid receptor is limited. Based on population pharmacokinetic (PK) analysis of the Phase III efficacy studies (Studies K4 and K5), <2% of patients will have exposures above the K_i for the δ-opioid receptor.

Naloxegol was tested at more than 300 non-opioid targets. No significant activity was noted at any of these targets, including the opioid receptor-like 1, and including approximately 90 targets directly or indirectly related to the CV system (eg, adrenergic, adenosine, dopamine, histamine, and muscarinic) at concentrations of at least 80-fold higher than exposures at 25 mg.

5.2 Naloxegol PK profile

Naloxegol undergoes rapid absorption with peak mean plasma concentrations attained <2 hours after single doses of 5 mg to 1000 mg, and twice daily doses of 25 mg to 250 mg for up to 8 days. At both 12.5 mg and 25 mg, mean terminal elimination half-life values were approximately 10 hours. At the therapeutic dose of 25 mg, significant antagonism of peripheral μ-opioid receptors (ie, free concentrations above K_i) is expected for approximately 15 hours. Naloxegol exposure is dose proportional from 8 mg to 1000 mg. Following multiple dosing, steady state is achieved within 2 to 3 days, and minimal accumulation is observed with once daily dosing. The predicted steady-state exposure in patients with OIC is approximately 30% higher than that observed in volunteers.

Based on in vitro studies, at concentrations achieved at therapeutic doses, naloxegol is not a modulator of metabolic enzymes or transporters, and has little potential to alter the PK of other drugs. The PK of naloxegol is affected by food and cytochrome P450 (CYP) 3A4/P-gp modulators. In addition, other extrinsic and intrinsic factors affecting the PK of naloxegol have been well characterized in the clinical pharmacology program. These points are detailed here:

- Increased bioavailability of naloxegol was observed when given with food (approximately 45% increase for area under the plasma concentration time curve from 0 to infinity and approximately 30% for C_{max}).
- Naloxegol is metabolized mainly by CYP3A4 enzymes and is a substrate of the P-gp transporter. In drug-drug interaction studies, concomitant administration of strong and moderate CYP3A4/P-gp inhibitors significantly increased the exposure of naloxegol (approximately 10-fold for strong inhibitors, and 2- to 5-fold for moderate inhibitors).
- Other factors (eg, age, gender, race, weight, hepatic impairment, laxative responder status, baseline opioid strength and dose, and creatinine clearance) have little impact on the PK of naloxegol.

The primary route of naloxegol elimination is via hepatic metabolism, with renal excretion playing a minimal role. Although renal clearance is a minor route of elimination, in the renal impairment study, up to 10-fold increases in the exposure of naloxegol were observed in 2 of 8 patients (in both the moderate and severe renal impairment groups, but not in the end-stage renal failure group).

The absolute bioavailability in humans has not been determined. The absolute bioavailability ranged from 7% to 21% in dogs and was 2% in the monkey; however, naloxegol was well absorbed orally in the rats.

The major plasma-circulating species is naloxegol. In the human metabolism study, 6 metabolites were found in feces, urine, and plasma. None of the individual metabolites has systemic exposure >10% of drug-derived material, and none were unique to humans, thus, based on International Conference on Harmonisation guidance (ICH M3(R2) 2009), naloxegol has no human circulating metabolites requiring further nonclinical characterization. There was no complete loss of the PEG-chain on any of the metabolites; therefore, the metabolites would also be expected to have reduced passive permeability/transport across the BBB and limited entry into the CNS compared to naloxone.

5.3 Naloxegol's capacity to cross the BBB and pharmacodynamic effects

In the nonclinical setting, naloxegol has been shown to be a substrate of P-gp and to have a limited capability to cross the BBB. In Caco2 cells, naloxegol has an efflux ratio of 15.4, which is greater than that of naloxone (approximately 1) and reduces to close to 1 in the presence of a range of P-gp inhibitors. In the presence of these inhibitors, the intrinsic permeability can be assessed, and this was shown to be at least 10-fold lower than for naloxone in the same system. Naloxegol has thus been shown to have a lower intrinsic permeability than naloxone and to be a P-gp substrate; both of which would be expected to reduce CNS exposure in vivo.

The minimal ability for naloxegol to cross the BBB was demonstrated in the rat quantitative whole body radiography study where the radioactivity concentrations in the brain and spinal cord were approximately 30-fold lower in the brain than in the blood. The limited CNS distribution was also confirmed in rat brain perfusion studies, which demonstrated a slower rate of entry into the brain for naloxegol (4.1 pmol/g brain/s compared to naloxone (60.2 pmol/g brain/s). In this model, the entry of naloxegol was similar or comparable to the slow permeation reference atenolol (5.17 pmol/g brain/s), which is used in humans as a non-brain-penetrating beta-blocker.

In healthy volunteers, assessments of peripheral and central μ-opioid receptor antagonism via morphine-induced delay in orocecal transit time (OCTT) and morphine-induced miosis indicated that naloxegol at doses from 15 mg to 125 mg antagonizes peripheral opioid effects on the GI tract without antagonizing opioid effects on the CNS. At doses >125 mg, possible partial reversal of morphine-induced miosis was observed in 2 of 17 subjects (1 who received naloxegol 250 mg and 1 who received naloxegol 1000 mg). The morphine-induced delay in OCTT was reversed by naloxegol in a dose-ordered fashion with an apparent plateau at doses ≥125 mg. At naloxegol doses ≥15 mg, ≥50% of subjects responded with at least a 25% improvement in OCTT, supporting the peripheral effect of naloxegol at therapeutic doses.

In a drug-drug interaction study, co-administration of naloxegol and the strong P-gp inhibitor quinidine did not antagonize the morphine-induced miosis effect (at morphine doses of 5 mg/70 kg, intravenous), indicating that, at the therapeutic dose of 25 mg¸ P-gp inhibition at the BBB does not result in CNS penetration of naloxegol.

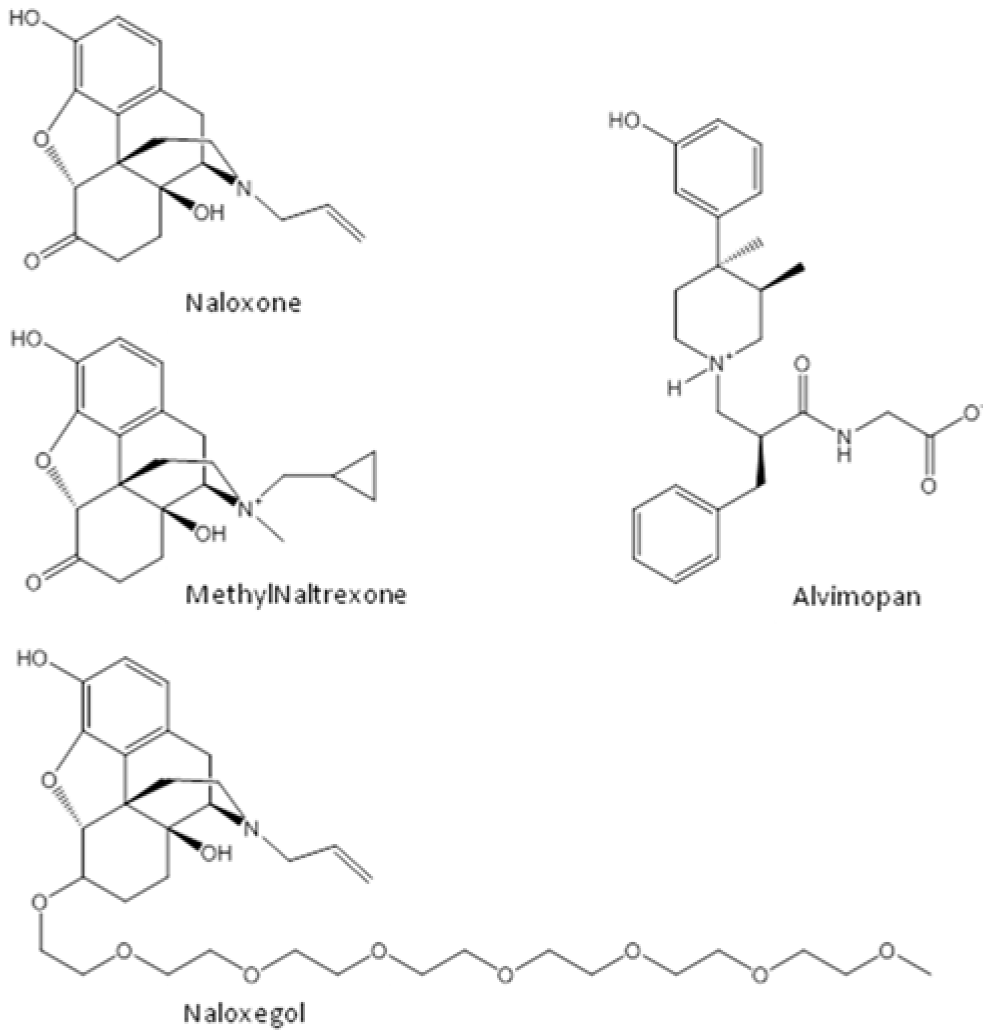
5.4 Differences among PAMORAs

Although μ-opioid-receptor antagonists may share a similar mechanism of action, there are structural and pharmacological differences that preclude extrapolation of observed risks from 1 molecule to others. Review of publicly available data on peripherally acting μ-opioid receptor antagonists (PAMORAs) indicates that there are differences between naloxegol and alvimopan. Differences in structure, metabolism, and opioid receptor subtype binding and selectivity warrant that, for approval, each PAMORA should be independently evaluated for benefit-risk ratio, including potential CV risk.

5.4.1 Structure

As shown in Figure 6, naloxegol, naloxone, and methylnaltrexone have morphinan ring-based structures, while alvimopan (and its major active metabolite, not displayed in Figure 6), a phenylpiperidine derivative, is similar in structure to meperidine (Demerol).

Figure 6 Chemical structures of naloxone, methylnaltrexone, naloxegol, and alvimopan



5.4.2 Metabolism

None of the 6 naloxegol metabolites found in feces, urine, and plasma were unique to humans, and none of the individual metabolites has systemic exposure >10% of drug-derived material. The activity of naloxegol metabolites has not been investigated. The major circulating species in plasma is naloxegol.

Naloxone is known to be glucuronidated, but only limited information is available.

The metabolism of methylnaltrexone in humans produces 3 metabolites; the 3-sulfate and the 6α- and 6β-alcohols generated by reduction of the ketone. These are all present in the circulation at concentrations lower than methylnaltrexone (Chandrasekaran et al 2010).

Alvimopan is metabolized in humans to the major metabolite ADL 08-0011 that has 3-fold greater sustained systemic exposure than alvimopan. ADL 08-0011 is also an equipotent (μ-opioid receptor) active metabolite (based on Alvimopan Summary Basis of Approval 2008).

5.4.3 Opioid receptor subtype binding and selectivity

A higher binding affinity (K_i) reflects lower K_i; therefore, as shown in Table 17, based on internal membrane binding assay data, naloxegol's affinity for the μ-opioid receptor is similar to that of κ-opioid receptor and much greater than that for the δ-opioid receptor. Naloxegol did not show any activity at more than 300 non-opioid targets (for more information, see Section 5.1).

Based on Beattie et al 2007, the opioid-receptor selectivity profile for other morphinans, naloxone, and methylnaltrexone is similar to that of naloxegol. Different sets of data suggest different affinities and different selectivity for alvimopan (Table 17). The physiological effects of opioids are primarily mediated by 3 well-characterized opioid receptors, μ-, δ-, and κ-opioid receptors, which are distributed throughout the body. Based on literature evidence from in vitro and in vivo nonclinical studies, Table 16 provides an overview of opioid receptor expression and their main function, and Table 17 provides an overview of the K_i of μ-opioid antagonist compounds.

Naloxegol, naloxone, and methylnaltrexone are neutral antagonists at the μ-opioid receptor, while modest inverse agonist activity has been reported for alvimopan and ADL 08-0011 at the δ- and μ-opioid receptors in vitro (Beattie et al 2007). Alvimopan has also been reported to have slow dissociation kinetics compared to naloxone and methylnaltrexone at the μ-opioid receptor in vitro (Cassel 2005).

Table 17 Overview of K_i of μ-opioid antagonists

Opioid receptor type	μ-opioid receptors	κ-opioid receptors	δ-opioid receptors
K_i (nM) to opioid receptors			
Naloxegol[a]	7.42	8.65	203.0
Naloxone[b]	0.63	2.00	12.60
Methylnaltrexone[b]	10.00	31.62	631.0
Alvimopan[b]	0.25	5.00	2.51
Alvimopan major metabolite[b]	0.25	32.00	16.00
Alvimopan[c]	0.44	10.00	100.0
Alvimopan major metabolite[c]	0.81	110.0	290.0

a Based on membrane binding assay data.
b Based on Anissian et al 2012, Beattie et al 2007, and Beattie 2009.
c Based on Alvimopan Summary Basis of Approval 2008.
K_i Binding affinity.

6. POTENTIAL OF NALOXEGOL TO PRODUCE OPIOID WITHDRAWAL

The minimal ability for naloxegol to cross the blood-brain barrier (BBB) was demonstrated in the rat quantitative whole body radiography study, in which the radioactivity concentrations in the brain and spinal cord were approximately 30-fold lower in the brain than in the blood. The limited central nervous system (CNS) distribution was also confirmed in rat brain perfusion studies, which demonstrated a slower rate of entry into the brain for naloxegol (4.1 pmol/g brain/s) compared to naloxone (60.2 pmol/g brain/s), and equivalent to the slow permeation reference atenolol (5.17 pmol/g brain/s). In healthy volunteers, assessments of peripheral and central μ-opioid receptor antagonism via morphine-induced delay in oral cecal transit time and miosis indicated that naloxegol (at doses from 15 mg to 125 mg) antagonizes peripheral opioid effects on the gastrointestinal (GI) tract without antagonizing opioid effects on the CNS. At doses >125 mg, possible partial reversal of morphine-induced miosis was observed in 2 of 17 subjects (1 who received naloxegol 250 mg and 1 who received naloxegol 1000 mg).

6.1 Opioid withdrawal

Opioid withdrawal (OWD) syndrome consists of a cluster of non-specific symptoms and is often described as a flu-like, non-life-threatening illness. OWD is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as a constellation of 3 or more withdrawal symptoms developing within minutes to several days after cessation of prolonged opioid use or administration of a centrally acting opioid antagonist after a period of opioid use (American Psychiatric Association 2013). The OWD syndrome as described in the DSM-5 is considered to be primarily related to centrally mediated mechanisms, although both peripheral and central μ-opioid receptors are thought to be involved in the manifestation of the syndrome. The following symptoms and signs are listed in the DSM-5 for OWD syndrome: dysphoric mood, nausea, vomiting, muscle aches, lacrimation, rhinorrhea, pupillary dilation, sweating, piloerection, diarrhea, yawning, fever, and insomnia. Although the syndrome itself was first described more than 70 years ago (Himmelsbach 1941), it has not been established whether the individual withdrawal symptoms arise via peripheral or central mechanisms, or perhaps via both. The only exception may be pupillary dilation, which is considered to be centrally mediated and is often used as a test for the potential of a μ-antagonist to cross the BBB and reverse central opioid effects.

GI symptoms and hyperhidrosis, which are both symptoms of OWD syndrome, have been reported in the literature in association with the use of peripheral μ-opioid antagonists (Thomas et al 2008, Michna et al 2011, Irving et al 2011). Consequently, given the mechanism of action of peripheral μ-opioid antagonists, an OWD-like syndrome could be expected to result from the actions of these drugs at the peripheral μ-opioid receptors but not in the CNS. In accordance with these data, in the naloxegol Phase III program, higher rates of GI adverse events (AEs) and hyperhidrosis were seen in the naloxegol-treated patients compared with placebo or Usual Care patients (Section 3.5.2). The most common AEs, including GI AEs, in Phase III program are listed in Table 7. The potential links between OWD and cardiovascular (CV) effects are discussed in Section 7.

There are no epidemiological data on the frequency of OWD in clinical populations. It can be assumed to be relatively common given that approximately 3% of the United States population are estimated to be receiving chronic opioid therapy (Sullivan et al 2005) and are, thus, at risk for OWD if they interrupt treatment or reduce their dose. In clinical trials of long-term opioid treatment, rates of OWD up to 10% have been reported depending on the trial methodology (Hale et al 2010).

6.2 Evaluation of the potential of naloxegol to produce OWD in Phase III studies

The approaches to the characterization of the potential for naloxegol to precipitate OWD syndrome were extensive and included:

- AEs of OWD reported by Investigators based on Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for drug withdrawal syndrome (Section 6.3).

- A supportive post hoc programmatic analysis (without clinical interpretation) to further investigate OWD in the Phase III program was conducted to identify any patient with at least 3 of the DSM-5 symptoms reported as an AE occurring within a 1-week window at any time during the study in the Phase III studies (Section 6.4). The primary purpose of this analysis was to identify any additional potential cases for the assessment of whether linkage exists between OWD symptoms and CV effects. The DSM-5 criteria for defining OWD were followed, including consensus symptoms and their specific concurrence. The results of this analysis are presented in this section. The results of the CV analyses in these patients are presented in Section 7.1.

- A prespecified assessment utilizing the modified Himmelsbach scale (mHS) (Section 6.5). The mHS is a clinician observer-rated scale, in which patients are rated with respect to the 8 potential signs of withdrawal (ie, yawning, lacrimation, rhinorrhea, perspiration, tremor, mydriasis, piloerection, and restlessness) and quantified on a scale from 0 to 3 for each (0 [none], 1 [mild], 2 [moderate], and 3 [severe]), as observed at the time of the assessment during each visit (Culpepper-Morgan et al 1992, Himmelsbach 1941, Slatkin et al 2009, Webster et al 2008). In the composite score (ranging from 0 to 24), higher values indicate greater severity of symptoms. The mHS was chosen because this scale evaluates non-GI withdrawal signs only. Naloxegol's known GI effects could confound the assessment of OWD and erroneously imply a central withdrawal syndrome based solely on actions in the GI tract. The mHS was administered periodically in the Phase III studies, including at baseline before taking investigational product, and then again at 2 hours after first dose of investigational product (corresponding to the approximate maximum plasma drug concentration of naloxegol).

- Changes in the opioid dose and Numeric Rating Scale (NRS) pain scores as general indices of the potential for naloxegol to antagonize central opioid effects. In the 12-week pivotal studies, NRS was collected daily in an electronic diary by asking the patient to rate their pain (average and worst) over the past 24 hours on a scale from 0 (no pain) to 10 (worst pain imaginable). Changes in the daily opioid dose were assessed by monitoring the breakthrough and maintenance opioid use throughout the studies.

Assessment of potential association between OWD symptoms and CV effects is discussed in Section 7.

6.3 Assessment of patients with Investigator-reported AEs of OWD syndrome

A total of 13 withdrawal AEs were reported by Investigators in the naloxegol Phase III program, in which a total of 1386 patients were exposed to naloxegol and 700 patients to placebo or Usual Care. There were more Investigator-reported AEs of OWD in the naloxegol 25 mg group (9 patients, 0.9%) than in the comparator (placebo or Usual Care; 1 patient, 0.1%) or naloxegol 12.5 mg (3 patients, 0.7%) groups based on the total Phase III population (combining the placebo-controlled studies with the open-label, long-term safety study). See Table 18 for an overview of patients with OWD AEs and Appendix Table 27 for a detailed review of these AEs by pool. The verbatim terms reported by the Investigators were 9 opiate withdrawals, 2 narcotic withdrawals, 1 morphine sulphate withdrawal, and 1 drug withdrawal syndrome. All AEs were coded to the MedDRA preferred term drug withdrawal syndrome and are referred throughout this document as OWD AEs.

Of the 13 OWD AEs reported in the Phase III program, all were reviewed post hoc and 6 were not considered attributable to treatment with study drug. Of these 6 AEs, 2 were reported at least 3 days after stopping naloxegol and 4 were accompanied by a concurrent cessation/reduction of opioid dose or treatment with naloxone and; therefore, had attributable reasons for withdrawal other than the use of the investigational product (Appendix Table 27).

Thus, the remaining 7 OWD AEs were considered attributable to treatment with investigational product (0.1%, 0.2%, and 0.5% for the placebo/Usual Care, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively, overall incidence across the Phase III program). All of these events were reported with a constellation of OWD symptoms by the Investigator (Appendix Table 27). The 5 cases reported for the 25 mg group were noted to have GI symptoms at the time of the OWD (eg, diarrhea, vomiting, abdominal pain, and abdominal cramping) and various other non-GI symptoms.

Of note:

- All 7 OWD AEs occurred within the first 3 days of dosing of investigational product.
- None of the 7 OWD AEs were serious adverse events (SAEs), and all cases resolved without sequelae.
- Of the 7 OWD AEs, 2 were reported as the cause for discontinuation of investigational product (1 on placebo and 1 on naloxegol 25 mg), while 1 additional patient in the 25 mg group discontinued due to diarrhea that occurred concurrently with their OWD AE.

All of the attributable cases of OWD occurred in the placebo-controlled studies. There were no attributable cases of OWD in the controlled long-term safety study (Study K8), with more than 500 patients exposed to naloxegol 25 mg.

Table 18 Number (%) of patients with prespecified AEs of OWD syndrome during the study (placebo-controlled pool and Study K8)

	Placebo-controlled pool (Studies K4/K7 and K5)			52-week safety study (Study K8)	
	Placebo (N=444)	**NGL 12.5 mg (N=441)**	**NGL 25 mg (N=446)**	**Usual Care (N=270)**	**NGL 25 mg (N=534)**
OWD at any time	**1 (0.2)**	**3 (0.7)**	**6 (1.3)**	0	3 (0.6)
SAE	0	1 (0.2)	1 (0.2)	0	0
DAE	1 (0.2)	0	1 (0.2)	0	0
Severe intensity	0	0	1 (0.2)	0	2 (0.4)
OWD not attributable to investigational product[a]	**0**	**2 (0.5)**	**1 (0.4)**	**0**	**3 (0.6)**
OWD attributable to investigational product[b]	**1 (0.2)**	**1 (0.2)**	**5 (1.1)[c]**	**0**	**0**
SAE	0	0	0	0	0
DAE	1 (0.2)	0	1 (0.2)	0	0
Severe intensity	0	0	1 (0.2)	0	0

a Considered not attributable because the OWD event occurred during the post-treatment period (2 patients), with concurrent interruption of opioid treatment or treatment with a central opioid antagonist (4 patients).
b Considered attributable because the OWD event occurred with no concurrent interruption of opioid treatment or treatment with a central opioid antagonist.
c All 5 of these patients had concurrent gastrointestinal AEs. Four were on methadone.
AE Adverse event; DAE Discontinuation of investigational product due to an AE; N Number of patients in safety population; NGL Naloxegol; OWD opioid withdrawal; SAE Serious adverse event.

6.4 Additional DSM-5-based post hoc analysis for identification of potential OWD cases

The additional programmatic post hoc DSM-5 analysis excluded Investigator-reported OWD AEs and was conducted to identify potential additional AEs of OWD. Consistent with the Investigator-reported OWD AEs, results of this post hoc analysis showed the DSM-5-based events to be uncommon but occur more frequently with naloxegol than with placebo. The DSM-5 definition criteria and a list of AEs corresponding to the symptoms outlined in the DSM-5 for OWD are provided in Section 12.8.

This DSM-5 analysis identified a total of 6 additional potential cases in which 3 or more OWD symptoms reported as AEs were present within a 1-week window (Appendix Table 29).

- All of these cases occurred in naloxegol-treated patients (2 cases on naloxegol 12.5 mg and 4 on naloxegol 25 mg).

- One patient (naloxegol 25 mg) reported AEs leading to discontinuation (diarrhea, sweating, and nausea, all on Day 1). None were reported as SAEs.
- Four of the 6 patients reported AEs starting within the first week of dosing.
- Five of the 6 patients reported GI AEs.

6.5 Assessments using the mHS

Results of the mHS were similar across the treatment groups for all time points, including the assessment after the initial dose of naloxegol. This finding demonstrates that, in the Phase III program, naloxegol had a low propensity to precipitate withdrawal outside of the GI tract.

Mean change from baseline in mHS composite score was similar across treatment groups for the 12-week studies (Studies K4 and K5) and for the 52-week Study K8. Data for the 2 hours after-first-dose assessment and the last on-treatment assessment are presented in Table 19.

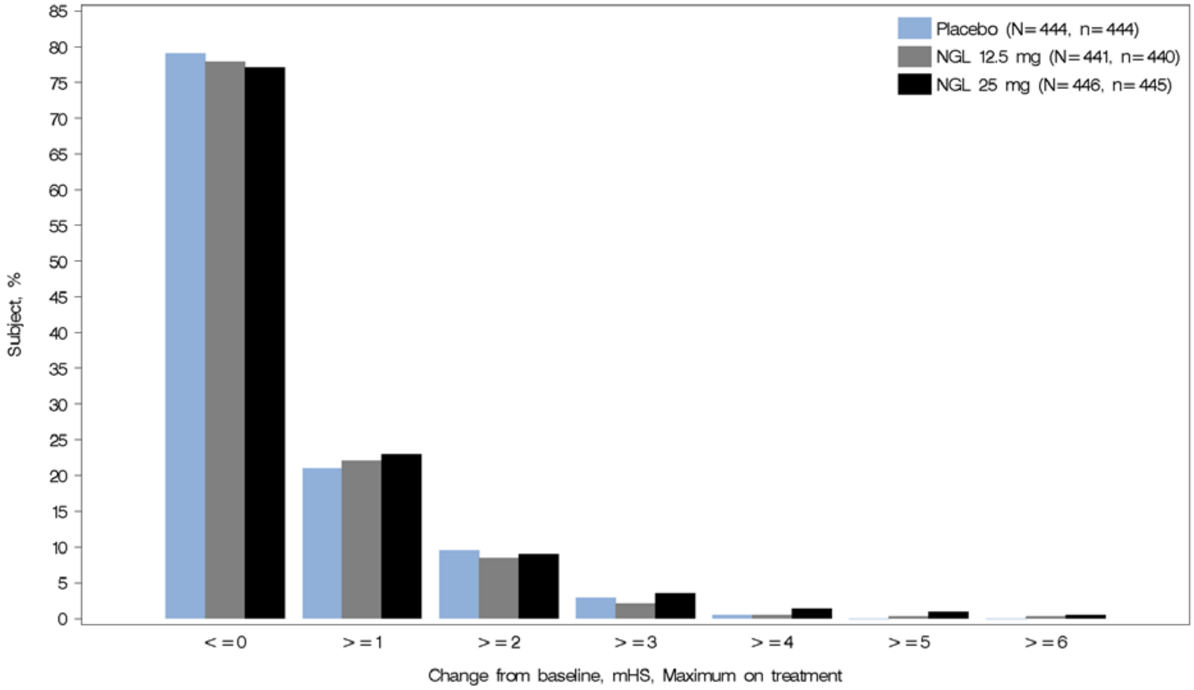
Table 19 Mean (SD) change from baseline in mHS (12-week pool and Study K8)

	12-week pool (Studies K4 and K5)			52-week safety study (Study K8)	
Time point	**Placebo (N=444)**	**NGL 12.5 mg (N=441)**	**NGL 25 mg (N=446)**	**Usual Care (N=270)**	**NGL 25 mg (N=534)**
2 hours after-first-dose[a]	0.02 (0.512)	-0.02 (0.625)	0.11 (0.768)	0.0 (0.52)	0.0 (0.65)
Last on treatment	-0.01 (0.751)	-0.09 (0.881)	-0.05 (0.842)	-0.1 (0.91)	-0.1 (0.84)

[a] The results shown for the 2 hours after-first-dose assessment in Study K8 are for the newly randomized patients only.
Scale: 0=none, 1=mild, 2=moderate, 3=severe.
mHS modified Himmelsbach scale scores; N Total number of patients with non-missing baseline and post-baseline mHS scores; NGL Naloxegol; SD Standard deviation.

Categories of change are presented in Figure 7 for the maximum change from baseline in mHS score while on treatment in the 12-week studies (maximum possible change=24). For most patients, there was no change from their baseline mHS scores at any point throughout the study. In the 12-week studies, 79.1%, 78.0%, and 77.1% of the patients in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively, had no increase from baseline at any assessment during the study. In the 52-week Study K8, 63.4% and 63.7% of the patients in the Usual Care and naloxegol 25 mg groups, respectively, had no increase from baseline at any assessment during the study.

Figure 7 Maximum change from baseline in mHS score on treatment (Studies K4 and K5)



mHS: modified Himmelsbach Scale. Percentages are based on the number of patients (n) with non−missing baseline and post−baseline score in each treatment group.

mHS Modified Himmelsbach scale.

6.6 Pain scores and opioid doses in naloxegol Phase III studies

To provide another assessment of the potential for naloxegol to antagonize opioid receptors in the CNS, changes in pain intensity (NRS) and opioid dose were assessed in the Phase III clinical program.

Comparison of the naloxegol groups with the placebo group indicates no differences in change from baseline in NRS scores (Appendix Table 24) or in daily opioid dose (Appendix Table 25) over Weeks 1 to 12 in Study K4 or Study K5. The proportions of patients with increases in NRS mean weekly pain score ≥2 (37/444 [8.3%] on placebo, 35/441 [7.9%] on naloxegol 12.5 mg, and 43/446 [9.6%] on naloxegol 25 mg) or in opioid dose ≥30% (24/444 [5.4%] on placebo, 17/441 [3.9%] on naloxegol 12.5 mg, and 28/446 [6.3%] on naloxegol 25 mg) at any time over the 12-week treatment period were similar across the groups. An analysis of the outlier data for the increase in weekly NRS mean pain score and for the increase in weekly opioid dose is presented in Figure 9 and Figure 10, respectively.

7. POTENTIAL LINKS BETWEEN OPIOID WITHDRAWAL AND CARDIOVASCULAR EFFECTS

The Food and Drug Administration (FDA) has expressed concern that peripherally acting μ-opioid-receptor antagonists may cause opioid withdrawal (OWD), which may precipitate cardiovascular (CV) events through a hemodynamic response. The effects of opioids and opioid antagonists on the CV system are complex and incompletely understood. A summary of literature search to these topics is provided in Section 4.1.

Transient increases in blood pressure (BP) and pulse have been reported during a central OWD (Charney et al 1984, Walsh et al 2003). Based on animal data, the effects on BP appear to be largely driven by CNS hyperactivity (Buccafusco 1990). In addition, there have been rare case reports of reversible stress cardiomyopathy in medically compromised patients undergoing OWD (Rivera et al 2006, Spadotto et al 2013), and a report of 7 serious complications (including 2 deaths) of rapid opioid detoxification conducted under anesthesia and using high doses of naloxone (Centers for Disease Control and Prevention 2013).

In the naloxegol Phase III clinical program, there were no patients with an OWD event (either Investigator-reported OWD or post hoc Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5] case) who had an event of major adverse cardiovascular event (MACE), CV serious adverse events (SAEs), or adverse events (AEs) related to BP, including syncope (Section 7.1). Increases in BP and pulse were similar between the naloxegol and placebo and Usual Care groups (Section 4.3). There were no notable increases in BP and pulse in the first week of dosing in patients who had Investigator-reported OWD (Appendix Table 28).

7.1 Lack of association of OWD with CV effects in naloxegol Phase III studies

No association was seen in the naloxegol Phase III clinical program between OWD (19 patients with either Investigator-reported OWD AEs or patients meeting the DSM-5 criteria) and the occurrence of MACE, CV events, or hemodynamic changes.

To understand and address the FDA concern, AstraZeneca analyzed the Phase III data for any association between patients who had potential OWD AEs and CV effects and reviewed all patients:

- Who had Investigator-reported OWD AEs or who met DSM-5-based criteria for OWD, and
- With MACE, CV SAEs, or CV AEs.

None of the 9 cases of MACE (Section 4.3.2) occurred in any of the 13 patients with Investigator-reported drug withdrawal syndrome events (OWD AEs; Section 6.3) or either of the 6 patients who met the DSM-5 criteria (Section 6.4).

The number of patients reporting MACE or Investigator-reported OWD AEs was low (9 patients in the Phase III program), and the rate of OWD AEs was approximately 1% in the naloxegol 25 mg group. As such, a definitive assessment of the potential correlation between 2 infrequent events is not possible. However, a review of these limited data did not provide evidence to support a link between these infrequent events. Of the 19 patients either meeting DSM-5 criteria or having Investigator-reported OWD AEs (13, 5 and 1 patients in the naloxegol 25 mg, naloxegol 12.5 mg, and placebo/Usual Care groups, respectively):

- none reported MACE events
- none reported CV SAEs or AEs
- none reported AEs related to changes in BP, including syncope.

Vital sign measurements were not done simultaneously with the reporting of AEs. However, in the patients with Investigator-reported OWD attributable to the investigational product, there were no notable changes in BP or pulse rate from baseline in the first week of dosing including after the first dose.

8. OTHER POTENTIAL PHYSIOLOGICAL LINKS BETWEEN OPIOID ANTAGONISTS AND CARDIOVASCULAR EFFECTS

This section discusses the potential mechanisms leading to major adverse cardiovascular events (MACE), possible roles of opioid antagonists that play in those mechanisms and, for each, relevant data for naloxegol.

Increased oxygen demand

An opioid antagonist causing tachycardia, increased blood pressure (BP), or even modest, simultaneous increases in both can result in ischemia in patients with coronary artery disease. Opioid antagonists with prominent central activity can lead to tachycardia and increased BP (van Dorp et al 2007); however, these effects do not characterize peripherally acting drugs. Although the naloxegol trial excluded patients with “cardiac concerns,” a substantial number of patients at risk for cardiovascular (CV) disease did participate (Section 3.3). Analysis of the collected vital signs data disclosed no hemodynamic signals for increased oxygen demand in patients taking naloxegol, for any of heart rate, BP, and rate-pressure product (Section 4.3.5).

Decreased oxygen supply

In nonclinical studies, naloxegol had no effect on heart rate, cardiac contractility, or coronary blood flow in the perfused, isolated, rat heart assay (Langendorff preparation at the highest concentration tested (10 µM, ≥81× human maximum plasma drug concentration [C_{max}]). Naloxegol also did not affect dog ventricle myocyte contractility (100 µM, ≥815× human C_{max}). In a single-dose dog telemetry study, changes in CV parameters (an increase in heart rate and decreases in arterial BP, left ventricular systolic pressure, and indices of cardiac contractility) were noted at exposures ≥6.7× higher than those achieved in the clinical studies at the proposed 25 mg dose. In repeat-dose toxicity studies in the dog (up to 9 months; at least 66× higher than human C_{max} at the proposed 25 mg dose), there were no effects on BP, heart rate, or electrocardiogram. Clinical data, including BP and pulse rate assessments within 1 hour to 2 hours after first dose, show that decreases in heart rate and BP occurred very rarely during the studies, as assessed by AEs and by the more objective vital signs data collected (Section 4.3).

Enhanced atherogenesis

Chronic administration of any agent could possibly accelerate the development of atheromatous plaque. Some agents, such as thiazide diuretics, increase total serum cholesterol and serum glucose, each of which associates with atherosclerotic disease (D'Agostino et al 2008, Brunner et al 2006), as does an increased C-reactive protein (Ridker et al 2009, Portenoy et al 2008, Puri et al 2013a). Coronary plaque narrows the vessel lumen, restricting blood flow and oxygen supply (Libby 2013). This mechanism applies not only to the coronary vasculature, with potential myocardial infarction (MI), but also to the cerebral vessels, with potential stroke (Amarenco and Labreuche 2009, Delaney et al 2012, Donnan et al 2008). The naloxegol nonclinical program did not include studies on atherogenic potential, and there was no signal from the chronic toxicity studies that indicated an atherogenic risk. The clinical program shows small changes in total cholesterol and glucose for all treatment groups, including placebo.

Rupture of coronary atheromatous plaque

Sudden extrusion of lipid-laden material or other endothelial vascular injury (Falk et al 2013) incites a vigorous platelet aggregatory response, often leading to complete vessel occlusion and termed "acute coronary syndrome" (Lemesle et al 2010, Libby 2009). The same mechanism in cerebral vessels results in acute ischemic stroke. Thrombus formation depends on platelet function (Wallentin et al 2009) and the balance between coagulation and fibrinolysis, all of which opioid antagonists and other drugs may influence. Potent anti-platelet and anti-coagulant drugs can all cause MACE via spontaneous intracerebral bleeding (ie, stroke). The nonclinical naloxegol program did not specifically investigate potential effects on platelet function, but there were no changes in the coagulation parameters (ie, activated partial thromboplastin and prothrombin time) in the dog repeat-dose toxicity studies or any signals in the repeat-dose toxicity program that indicated a specific risk. In the clinical program, no special tests of platelet aggregation were conducted. The clinical program discloses no abnormalities for routine hematologic measurements of platelet count, prothrombin time, and international normalized ratio.

Coronary vasospasm

Sudden constriction of a coronary artery may occur from withdrawal of vagal tone or a change in sympathetic activity (Stern and de Luna 2009), either of which can theoretically accompany administration of centrally acting opioid antagonists. Neither the nonclinical nor the clinical naloxegol program provides insight into the potential of naloxegol to induce coronary or cerebral vasospasm.

Altered ischemic pre-conditioning

Opioid receptors in the heart may modulate myocardial response to ischemia. Nonclinical models demonstrate smaller infarct size, but not infarct prevention, in the presence, versus absence, of opioids after a sequence of limited then substantial inflow obstruction. Thus, this mechanism could potentially explain imbalances in morbidity and mortality from CV events but should not be the prime explanation for an underlying imbalance in the MI incidence in the alvimopan long-term safety study. Nonclinical opioid receptor studies link the delta receptor to this potential beneficial ischemic pre-conditioning effect (Dragasis et al 2013, Hanna et al 2010, Headrick et al 2012). One study suggested possible interference with ischemic pre-conditioning by intravenous naloxone (Tomai et al 1999). Importantly, naloxegol has a low affinity to the delta receptor: pharmacokinetic analysis of Phase III studies indicates that <2% of patients have exposures above its binding affinity.

Cerebrovascular ischemia and hemorrhage

MACE includes both ischemic and hemorrhagic stroke. The previous section and the next section present relevant information relating to these potential mechanisms.

Increased risk of cardiac dysrhythmias

Sudden cardiac death results from ventricular dysrhythmia; thus, a pro-dysrhythmic drug can result in MACE. Mechanisms include prolongation of ventricular repolarization (QT/ corrected QT interval [QTc] interval; K+ channel), decreased atrioventricular conduction (PR/PQ interval; Ca++ channel), or slowed ventricular activation (QRS duration; Na+ channel) (Zipes et al 2006).

Atrial fibrillation can result in left atrial thrombus and consequent thromboembolic stroke, as well as heart failure (Fuster et al 2011).

Nonclinical data suggest that naloxegol neither affects cardiac ion channel activity nor risks dysrhythmias: in nonclinical studies, there were no effects on the human ether-à-go-go-related gene (concentration of naloxegol resulting in 50% ion channel inhibition ≥2445× human C_{max}). Furthermore, there were no effects on any of the 7 cardiac ion channels tested at concentrations of up to of 100 μM (ie, ≥815× human C_{max}). In a single-dose dog telemetry study, there were no effects on electrophysiological parameters at concentrations ≥90× the human C_{max}. In addition, in repeat-dose toxicity studies in dogs (up to 9 months; ≥66× higher than human C_{max} at the proposed 25 mg dose), no effects were seen on electrophysiological CV parameters. Clinically, the thorough QT study disclosed no clinically relevant QTc prolongation or other electrocardiographic abnormalities. The clinical program disclosed no signal for dysrhythmias, including no reported cases of Torsades de Pointes, ventricular tachycardia, or other ventricular dysrhythmias in naloxegol-treated patients.

Electrolyte disorders

Drugs causing hyperkalemia or inciting renal damage leading to hyperkalemia can result in cardiac ventricular dysrhythmias or cardiac asystole. The naloxegol program contains ample data indicating no effects, compared to placebo or Usual Care, on either electrolytes or renal function, with the latter assessed by serum creatinine.

Salt and water retention

Impaired renal function with albuminuria increases CV risk (Gansevoort et al 2013). Inability to excrete sodium and water can cause or worsen heart failure by increasing intravascular volume (Nesto et al 2003). Heart failure could also ensue from decreases in left ventricular contractility, as caused, for example, by doxorubicin (Cardinale et al 2010), or from immunologic or more obscure causes of cardiomyopathy.

Drugs increasing myocardial contractility may worsen survival in patients with heart failure if accompanied by cardiac arrhythmias, increased oxygen consumption, and coronary hypoperfusion, causing myocardial ischemia and myocardial damage through calcium overload (Teerlink et al 2009).

In nonclinical studies of Naloxegol, including a renal function study in rats, there were no relevant observations related to this potential mechanism. The single-dose and repeat-dose dog studies, previously discussed, together generate no concern for a heart failure risk on the basis of altered inotropic state. Importantly, no increase in incidence of clinical heart failure was seen in naloxegol-treated patients compared to placebo or Usual Care patients in the 12-week and 1-year clinical program, respectively.

9. CONCLUSIONS

9.1 Naloxegol overall risk-benefit assessment

Patients with opioid-induced constipation (OIC) typically take opioids for years and suffer with the discomfort and associated symptoms of constipation. They experience daily the frustration of incomplete relief afforded by currently available treatment options (Warner 2012, Becker and Blum 2009, Bell et al 2009, Camilleri 2011).

OIC does not improve over time, and symptoms persist throughout the duration of opioid use (Warner 2012). Unrelieved constipation symptoms may add to the burden of pain and underlying illness and may dissuade patients from using the required analgesic dose to achieve effective pain relief (Camilleri 2011). Furthermore, a recent 500-patient survey concluded that OIC significantly impacts pain management in patients with non-cancer pain (Daniell 2011, Datto et al 2014). The need for new and effective therapies is especially apparent for patients who continue to have constipation symptoms despite treatment with laxatives (Becker and Blum 2009, Bell et al 2009, Mitchell et al 2004, Müller-Lissner et al 2013), a subgroup of patients that was prospectively defined for the naloxegol program as laxative inadequate responders and in which naloxegol was shown to provide benefit. Naloxegol, by binding to μ-opioid receptors within the gastrointestinal (GI) tract, targets the underlying causes of OIC. With its limited ability to affect opioid receptors located in the central nervous system (CNS) at therapeutic doses, naloxegol has been shown to alleviate OIC without reducing the central analgesic effects of opioids.

New therapeutic options for treating OIC that allow effective management of chronic pain is a meaningful clinical goal for patients. Naloxegol once daily oral therapy would help to address a clear unmet medical need by providing consistent and durable therapeutic gain for patients with OIC, including those with inadequate response to laxatives. Naloxegol has a mechanism of action (MoA) that was designed to directly address the underlying cause of OIC, without evidence of interference with the analgesic effect of opioids, as measured by Numeric Rating Scale (NRS) scores, in the clinical program. Overall, for patients already suffering from moderate to severe chronic pain requiring long-term opioid therapy, naloxegol may provide an effective treatment option and decrease their symptom burden with an acceptable safety and tolerability profile.

Naloxegol at therapeutic doses was generally safe and well tolerated in the target population in studies up to 52 weeks of treatment. The most common side effects include GI adverse events (AEs) (the most common of which were abdominal pain, diarrhea, nausea, and flatulence), which are generally mild and often subside with continued treatment. Opioid withdrawal (OWD) with naloxegol was uncommon and does not appear to be linked with serious sequelae.

Although the program was not designed or powered to rule out safety differences or increased risks for rare events, major adverse cardiovascular events (MACE) were infrequent and balanced across treatment groups: across the entire population, there was no notable imbalance between naloxegol and either placebo or Usual Care comparator for cardiovascular (CV) AEs or important hemodynamic and electrocardiographic changes, and through a prespecified adjudication process, no evidence for increased risk of MACE for naloxegol versus comparator was indicated.

The totality of naloxegol data provides evidence for durable and consistent benefits for most patients with OIC, which outweighs the observed risks.

9.2 Conclusions specific to Food and Drug Administration 4 topics of concern

Opioid antagonists and CV safety

- In the naloxegol Phase III clinical program, the incidence of MACE, CV serious adverse events (SAEs), CV AEs, and abnormal vital signs was low and similar across the treatment groups.
- Extensive clinical and post-marketing experience with μ-opioid-receptor antagonists (eg, naltrexone and naloxone, although for indications other than OIC) reveals that serious CV events with these compounds are rare.

Regarding the 4 topics the Food and Drug Administration (FDA) asked all sponsors to address, the following can be concluded:

1. Relevant pharmacology

- Naloxegol has high affinity for μ- and κ-opioid receptors and has low affinity for δ-opioid receptors. Naloxegol exposures at 25 mg are sufficient to antagonize μ- and κ-opioid receptors and are unlikely to antagonize δ-opioid receptors. In nonclinical tests, no significant activity was noted at more than 300 non-opioid targets, including approximately 90 targets directly or indirectly related to the CV system at concentrations of at least 80-fold higher than exposures at 25 mg.

- Naloxegol is a polyethylene glycol derivative of naloxone. Naloxegol has limited ability to cross the blood-brain barrier. Naloxegol was designed to act upon the μ-opioid receptor in the periphery, thereby, decreasing the constipating effects of opioids without interfering with the opioid-mediated analgesic effects on the CNS.

- Naloxegol does not have major circulating metabolites in humans.

- While the MoA for naloxegol is the same as other peripherally acting μ-opioid receptor antagonists, there are differences in chemical structure, circulating active metabolites, and receptor binding and selectivity, which warrant that, for approval, each PAMORA should be independently evaluated for benefit-risk ratio, including potential CV risk.

2. Potential to produce OWD

- Data from both the nonclinical and clinical program support that naloxegol has a low propensity to antagonize central opioid receptors and produce OWD syndrome. The investigations that support this conclusion included no relevant changes in the naloxegol versus control groups in the level of pain (as monitored using the NRS), changes in opioid doses, and objective scoring of non-GI OWD signs (modified Himmelsbach scale). However, in uncommon cases (approximately 1%), a constellation of GI and non-GI symptoms, identified by the Investigator as OWD, was reported. Due to the MoA of naloxegol, and its pharmacodynamic and physiologic effects (reversal of impaired GI motility and decreased intestinal fluid absorption), GI side effects are expected in some patients. These OWD AEs were observed shortly after initial administration, were more common in the naloxegol 25 mg group than in either the naloxegol 12.5 mg or placebo groups, and were not associated with serious medical sequelae.

3. Potential link between OWD and CV effects

- No association was seen between CV events and OWD. There were no patients with an OWD event (either Investigator-reported OWD or post hoc DSM-5 case) who had an event of MACE, CV SAEs or AEs, or syncope.

4. Other potential physiological links between opioid antagonists and CV effects

- MACE can occur from multiple mechanisms, including myocardial ischemia from increased oxygen demand, enhanced atherogenesis, electrolyte disorders, and salt and water retention. Indirect evidence generated in the naloxegol program related to these possible triggering mechanisms does not indicate an increased CV risk in the intended population. However, the naloxegol development program was not designed to specifically rule out all of these mechanisms.

9.3 Overall conclusions

The naloxegol clinical CV data appear to be different from the alvimopan long-term safety data, referenced by the FDA, even though neither dataset was powered for precisely estimating rare events. The reasons for these differences are not known but may be due to a chance imbalance observed in a small numbers of events and/or other unknown confounding differences in trial design or conduct. Alternatively, differences in clinical outcomes between alvimopan and naloxegol could be the consequence of differences in structure, metabolism, and/or differences in opioid subtype receptor binding affinity and selectivity between the molecules. Based on the totality of the information available, including nonclinical and clinical naloxegol cardiac safety data, a lack of a plausible biological mechanism, and additional analyses done to address the FDA's specific questions, AstraZeneca concludes that naloxegol treatment is unlikely to increase the CV risk among patients with OIC. Therefore, AstraZeneca concludes that the safety of naloxegol has been sufficiently characterized for approval.

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11. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
AUC	Area under the plasma concentration time curve from 0 to infinity
BBB	Blood-brain barrier
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum plasma drug concentration
CNS	Central nervous system
CV	Cardiovascular
CV-EAC	Cardiovascular Event Adjudication Committee
CYP	Cytochrome P450
DAE	Discontinuation of investigational product due to an adverse event
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
FDA	Food and Drug Administration
GI	Gastrointestinal
HR	Heart rate
K_i	Binding affinity
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
mHS	Modified Himmelsbach scale
MI	Myocardial infarction
MoA	Mechanism of action
Naloxegol	Also known as NKTR-118, PEG-naloxol, NKT-10018, naloxol 6α-methoxyhepta(ethylene glycol) ether, and α-6-mPEG7-O-naloxol. International Union of Pure and Applied Chemistry (IUPAC) name: 17-allyl-4,5α-epoxy-3,14-dihydroxy-6α-methoxyhepta(ethylenglycol) oxy-morphinan.
NDA	New Drug Application
NRS	Numeric Rating Scale
OCTT	Orocecal transit time

Abbreviation or special term	Explanation
OIC	Opioid-induced constipation
OWD	Opioid withdrawal
PAMORA	Peripherally acting μ-opioid-receptor antagonist
PEG	Polyethylene glycol
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
QTc	Corrected QT interval
QTcF	Fridericia QT interval
SAE	Serious adverse event
SBM	Spontaneous bowel movement; a bowel movement occurring at 24 hours or more from the time the patient last used rescue medication
SBP	Systolic blood pressure
US	United States
δ	Delta
κ	Kappa
μ	Mu

Note: Abbreviations used in tables and figures are defined in the table/figure footnotes.

12. APPENDICES

12.1 Disposition of patients

Table 20 and Table 21 provide a disposition of patients, in Studies K4 and K5, and Study K8, respectively.

Table 20 Patient disposition and discontinuation data, Studies K4 and K5 (all patients)

	Number of patients (%)					
	Study K4			Study K5		
Patient disposition	**Placebo**	**NGL 12.5 mg**	**NGL 25 mg**	**Placebo**	**NGL 12.5 mg**	**NGL 25 mg**
Randomized	217 (100.0)	217 (100.0)	218 (100.0)	233 (100.0)	233 (100.0)	234 (100.0)
Included in the ITT analysis set [a]	214 (98.6)	213 (98.2)	214 (98.2)	232 (99.6)	232 (99.6)	232 (99.1)
Received treatment	216 (99.5)	215 (99.1)	218 (100.0)	232 (99.6)	231 (99.1)	234 (100.0)
Included in the safety analysis set [a]	213(98.2)	211 (97.2)	214 (98.2)	231 (99.1)	230 (99.1)	232 (100.0)
Did not receive treatment	1 (0.5)	2 (0.9)	0	1 (0.4)	2 (0.9)	0
Completed the study (ITT analysis set)	177 (81.6)	174 (80.2)	173 (79.4)	187 (80.3)	177 (76.0)	173 (73.9)
Treated and discontinued study (ITT analysis set)	36 (16.6)	37 (17.1)	41 (18.8)	44 (18.9)	53 (22.7)	59 (25.2)
Subject decision	13 (6.0)	17 (7.8)	6 (2.8)	13 (5.6)	23 (9.9)	20 (8.5)
Eligibility criteria not fulfilled	1 (0.5)	0	0	1 (0.4)	0	0
Death	0	1 (0.5)	0	0	0	0
Adverse event	11 (5.1)	9 (4.1)	22 (10.1)	12 (5.2)	11 (4.7)	24 (10.3)
Severe non-compliance to protocol	2 (0.9)	0	5 (2.3)	2 (0.9)	2 (0.9)	2 (0.9)
Lack of therapeutic response	2 (0.9)	0	0	3 (1.3)	3 (1.3)	0
Study-specific withdrawal criteria	2 (0.9)	3 (1.4)	1 (0.5)	3 (1.3)	0	3 (1.3)
Lost to follow-up	4 (1.8)	7 (3.2)	6 (2.8)	9 (3.9)	11 (4.7)	9 (3.8)
Other	1 (0.5)	0	1 (0.5)	1 (0.4)	3 (1.3)	1 (0.4)
Patients continued into Study K7/Study K8[b]	104 (47.9)	95 (43.8)	98 (45.0)	30 (12.9)	26 (11.2)	22 (9.4)

[a] Patients who had previously or concurrently participated in the program at another center were excluded from the ITT and safety sets.
[b] The patients in Study K4 could continue into Study K7 and patients in Study K5 could continue into Study K8.
Note: The percentages are based on the number of patients randomized in each treatment group.
ITT Intent-to-treat; NGL Naloxegol.

Table 21 Patient disposition and discontinuation data, Study K8 (all patients)

	Number of patients (%)	
Patient disposition	**Usual Care**	**NGL 25 mg**
Randomized	281 (100.0)	563 (100.0)
Received treatment	281[a] (100.0)	559[a] (99.3)
Included in the safety analysis set [a]	270 (96.1)	534 (94.8)
Did not receive treatment	0	4[b] (0.7)
Completed the study (Safety analysis set)	189 (67.3)	327 (58.1)
Treated and discontinued study (Safety analysis set)	81 (28.8)	207 (36.8)
Subject decision	38 (13.5)	70 (12.4)
Eligibility criteria not fulfilled	5 (1.8)	9 (1.6)
Death	1 (0.4)	1 (0.2)
Adverse event	5 (1.8)	56 (10.0)
Severe non-compliance to protocol	2 (0.7)	8 (1.4)
Lack of therapeutic response	0	4 (0.7)
Study-specific withdrawal criteria	7 (2.5)	14 (2.5)
Lost to follow-up	19 (6.8)	36 (6.4)
Other	4 (1.4)	9 (1.6)

[a] A total of 36 patients who received treatment had either (a) previously or concurrently participated in the naloxegol program at another study center or (b) been randomized at 2 sites where related data quality issues were identified. These patients were excluded from the safety analysis set.

[b] Enrolled patients did not receive treatment due to patient decision (2 new patients in the naloxegol 25 mg group) and eligibility criteria not fulfilled (2 new patients in the naloxegol 25 mg group).

NGL Naloxegol.

12.2 Demographics in Study K8

Table 22 Demographic characteristics, Study K8 (Safety analysis set)

Demographic characteristics	NGL 25 mg (N=534)	Usual Care (N=270)
Age[a] (years)		
Mean (SD)	52.8 (10.09)	52.7 (10.24)
BMI (kg/m^2), n (%)		
≥30	267 (50.2)	149 (55.2)
Sex, n (%)		
Male	181 (33.9)	91 (33.7)
Female	353 (66.1)	179 (66.3)
Race, n (%)		
White	423 (79.2)	204 (75.6)
Black or African American	98 (18.4)	60 (22.2)
Asian	4 (0.7)	3 (1.1)
Native Hawaiian or Other Pacific Islander	0	0
American Indian or Alaska Native	4 (0.7)	1 (0.4)
Other	5 (0.9)	2 (0.7)
Primary reason for pain, n (%)		
Back pain	302 (56.6)	150 (55.6)
Joint pain	23 (4.3)	16 (5.9)
Fibromyalgia	38 (7.1)	16 (5.9)
Headache/migraine	1 (0.2)	2 (0.7)
Arthritis	46 (8.6)	24 (8.9)
Neuralgia	6 (1.1)	3 (1.1)
Pain syndrome	8 (1.5)	3 (1.1)
Other	110 (20.6)	55 (20.4)
Duration of current opioid use[b] (months)	N=532	N=267
Mean (SD)	47.9 (51.75)	50.2 (53.59)
Daily maintenance opioid dose (meu),[c] mean (SD)	147.3 (243.02)	137.2 (134.94)
Patient took a laxative over the past 2 weeks,[d] n (%)	368 (68.9)	169 (62.6)
Numeric Rating Scale scores at baseline	N=521	N=257
Mean (SD)	5.5 (1.69)	5.6 (1.74)

[a] Age is calculated as the rounded down integer value in years of ([date of consent–date of birth]/365.25).
[b] Baseline was assessed at enrolment.
[c] Calculated as the mean of the daily opioid doses (maintenance plus breakthrough) during the OIC confirmation period.
[d] Percentages are based on the number of patients in the safety analysis set in each treatment group and patient group.

Note: The percentages are based on the number of patients in the safety analysis set in each treatment group and patient group with non-missing data for the parameter.

BMI Body mass index; meu Morphine equivalent units; NGL Naloxegol; N Total number of patients; n Number of patients in a category; OIC Opioid-induced constipation; SD Standard deviation.

12.3 Most common adverse events in Study K8

Table 23 Number (%) of patients with the most common (≥2% incidence in any treatment group) AEs during the treatment period (Study K8)

Preferred term	Usual Care (N=270) n (%)[a]	NGL 25 mg (N=534) n (%)[a]
Any AE	194 (71.9)	428 (80.1)
Abdominal pain	9 (3.3)	95 (17.8)
Diarrhoea	16 (5.9)	69 (12.9)
Nausea	11 (4.1)	50 (9.4)
Back pain	24 (8.9)	48 (9.0)
Headache	13 (4.8)	48 (9.0)
Flatulence	3 (1.1)	37 (6.9)
Arthralgia	16 (5.9)	33 (6.2)
Nasopharyngitis	15 (5.6)	33 (6.2)
Upper respiratory tract infection	23 (8.5)	31 (5.8)
Bronchitis	12 (4.4)	30 (5.6)
Vomiting	15 (5.6)	27 (5.1)
Abdominal pain upper	3 (1.1)	27 (5.1)
Cough	7 (2.6)	26 (4.9)
Sinusitis	19 (7.0)	23 (4.3)
Urinary tract infection	22 (8.1)	22 (4.1)
Pain in extremity	8 (3.0)	20 (3.7)
Fall	12 (4.4)	19 (3.6)
Muscle spasms	8 (3.0)	17 (3.2)
Anxiety	4 (1.5)	17 (3.2)
Fatigue	3 (1.1)	17 (3.2)
Hyperhidrosis	1 (0.4)	17 (3.2)
Gastroenteritis viral	5 (1.9)	15 (2.8)
Insomnia	5 (1.9)	15 (2.8)
Nasal congestion	4 (1.5)	15 (2.8)
Depression	10 (3.7)	14 (2.6)
Pyrexia	6 (2.2)	14 (2.6)
Hypertension	9 (3.3)	13 (2.4)
Abdominal discomfort	1 (0.4)	13 (2.4)
Pneumonia	3 (1.1)	12 (2.2)

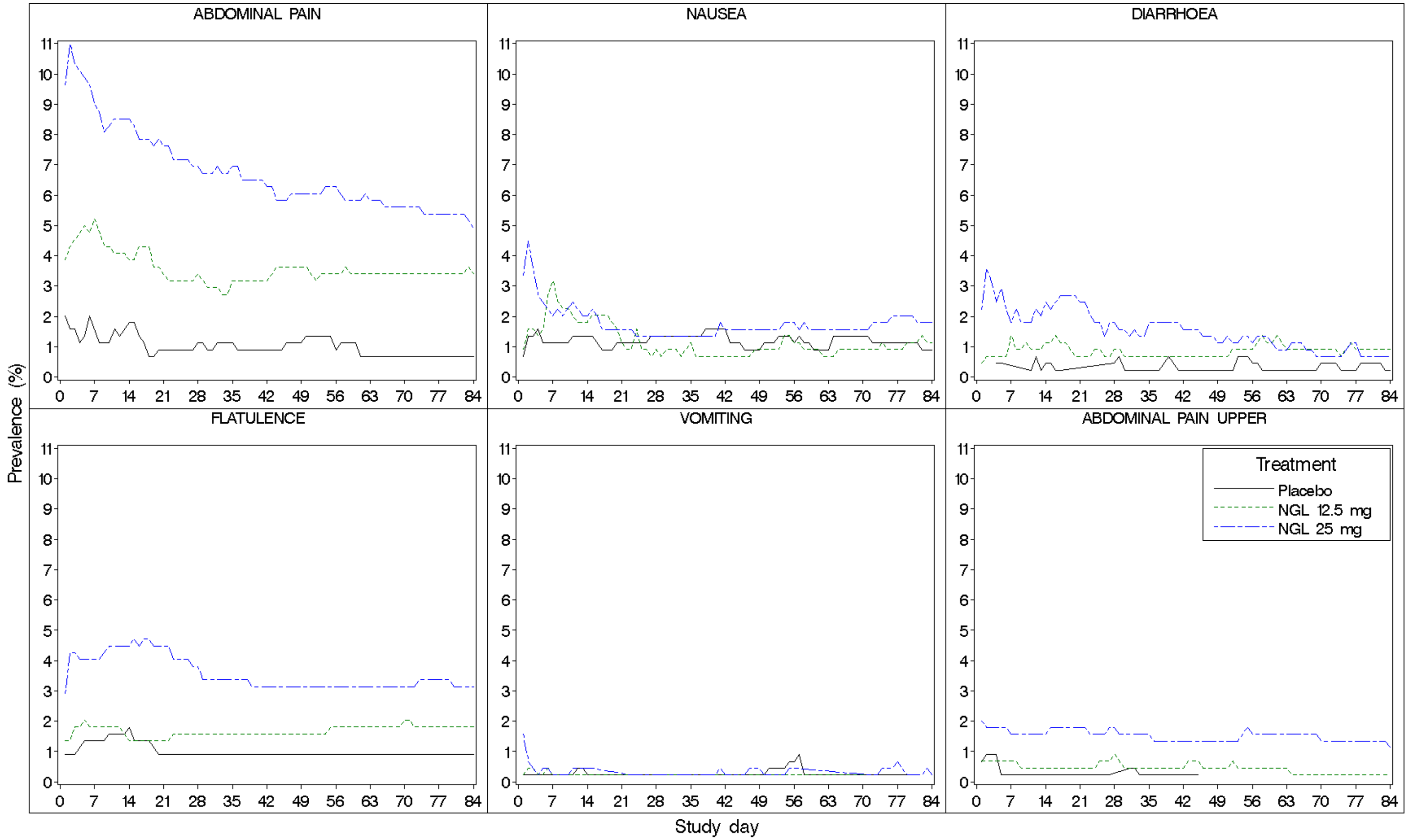
Table 23 Number (%) of patients with the most common (≥2% incidence in any treatment group) AEs during the treatment period (Study K8)

Preferred term	Usual Care (N=270) n (%)[a]	NGL 25 mg (N=534) n (%)[a]
Oedema peripheral	8 (3.0)	11 (2.1)
Dizziness	3 (1.1)	11 (2.1)
Chills	0	11 (2.1)
Influenza	8 (3.0)	10 (1.9)
Musculoskeletal pain	6 (2.2)	9 (1.7)
Anaemia	6 (2.2)	5 (0.9)
Hypercholesterolaemia	6 (2.2)	5 (0.9)
Asthma	7 (2.6)	3 (0.6)
Musculoskeletal chest pain	6 (2.2)	3 (0.6)
Dehydration	6 (2.2)	2 (0.4)

[a] The percentages are based on the number of patients in the safety analysis set in each treatment and patient group.
Note: AEs are coded using MedDRA version 15.0.
Note: AEs that started on or after the first dose of study drug (naloxegol 25 mg or Usual Care) through the day of the last dose of study drug are included.
Note: Patients are counted no more than once for incidence of PT.
Note: Sorted by PT in decreasing order of frequency (by total number on naloxegol 25 mg).
AE Adverse event; MedDRA Medical Dictionary for Regulatory Activities; N Total number of patients; n Number of patients in a category; NGL Naloxegol; PT Preferred term.

12.4 Incidence of common gastrointestinal adverse events over time (Studies K4 and K5)

Figure 8 Common GI AEs over time (Studies K4 and K5)



All percentages are based on the number of patients in the safety set at baseline. Most common is referring to the overall incidence.
Any events ongoing at study completion have duration calculated based on the imputation of the study completion date.

AE Adverse event; GI Gastrointestinal; NGL Naloxegol.

12.5 Numeric Rating Scale pain scores and opioid doses over time

Table 24 Analysis of change from baseline in NRS average pain scores over 12 weeks in Studies K4 and K5

Study	Group	N	LS mean change from baseline (SE)	Difference in LS means vs placebo	95% CI	P-value
	Placebo	212	-0.22 (0.08)	NA	NA	NA
K4	NGL 12.5 mg	211	-0.26 (0.08)	-0.03	(-0.24, 0.18)	0.773
	NGL 25 mg	213	-0.20 (0.08)	0.02	(-0.19, 0.23)	0.837
	Placebo	231	-0.07 (0.07)	NA	NA	NA
K5	NGL 12.5 mg	227	-0.10 (0.08)	-0.03	(-0.22, 0.16)	0.744
	NGL 25 mg	229	-0.02 (0.08)	0.05	(-0.13, 0.24)	0.572

Notes: Analysis via mixed model repeated measures. K4 mean baseline average NRS=4.67, K5 mean baseline average NRS=4.62.

CI Confidence interval; LS Least square; N Total number of patients; NA Not applicable; NGL Naloxegol; NRS Numeric Rating Scale; SE Standard error.

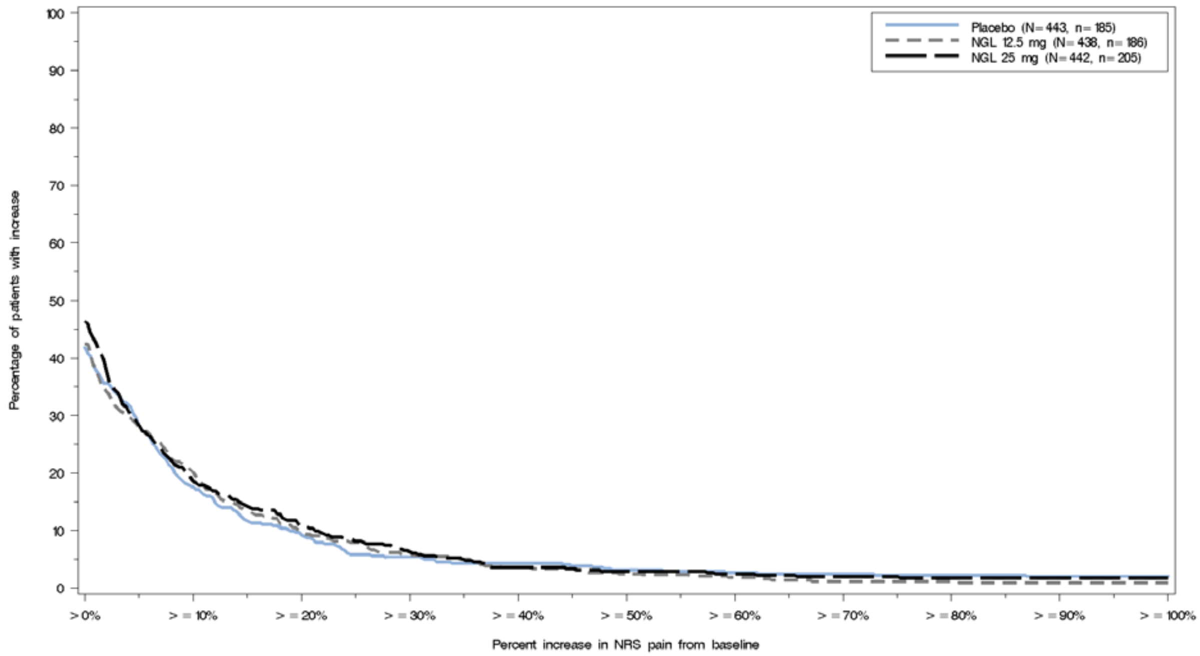
Table 25 Analysis of change from baseline in opioid dose over 12 weeks in Studies K4 and K5

Study	Group	N	LS mean change from baseline (SE)	Difference in LS means vs placebo	95% CI	P-value
	Placebo	213	-2.75 (1.88)	NA	NA	
K4	NGL 12.5 mg	211	-3.51 (1.90)	-0.76	(4.98, 3.46)	0.724
	NGL 25 mg	214	0.09 (1.90)	2.84	(-1.39, 7.07)	0.188
	Placebo	231	-0.84 (1.08)	NA		
K5	NGL 12.5 mg	230	-1.47 (1.09)	-0.63	(-3.54, 2.27)	0.669
	NGL 25 mg	232	-0.58 (1.11)	0.26	(-2.66, 3.17)	0.863

Notes: Analysis via mixed model repeated measures. K4 mean baseline daily opioid dose=138.09 meu, K5 mean baseline daily opioid dose=136.01 meu.

CI Confidence interval; LS Least square; meu Morphine equivalent units; N Total number of patients; NA Not applicable; NGL Naloxegol; SE Standard error.

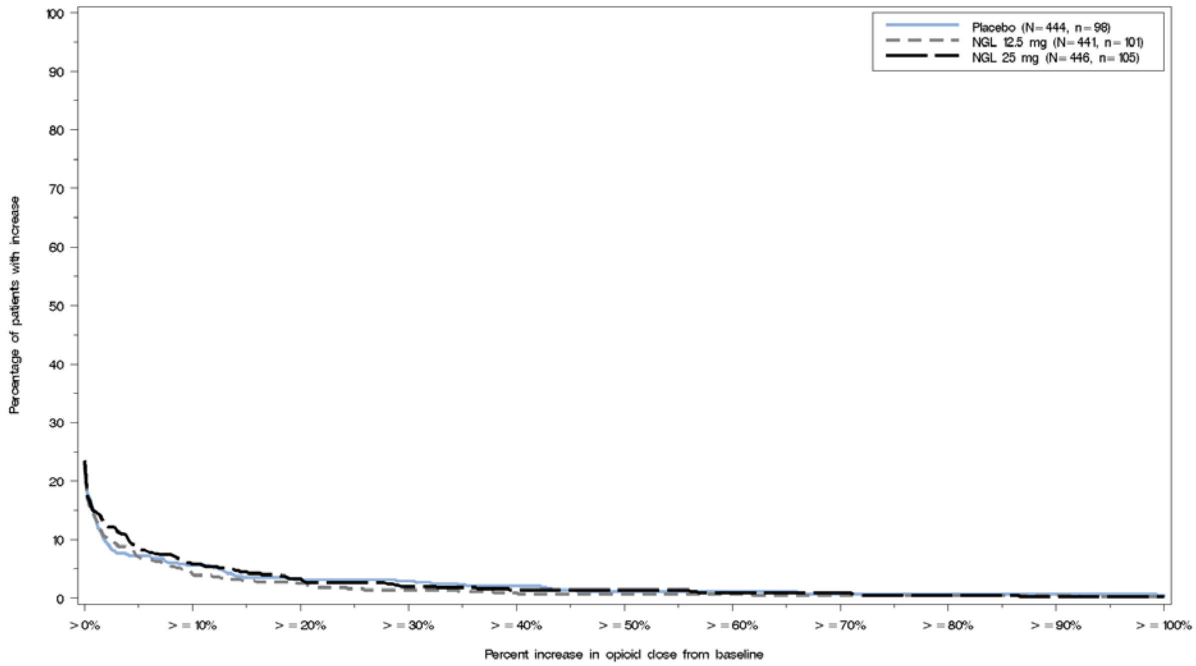
Figure 9 Percentage of patients by percent increase (worsening) from baseline in weekly NRS mean pain score, Weeks 1 to 12 (Studies K4 and K5)



Note: NRS average pain scores range from 0 (no pain) to 10 (worst imaginable pain). The y-axis presents the number of patients meeting the specific percentage increase from baseline score (x-axis) divided by the number (N) of patients with baseline and post-baseline assessments for each treatment group. The total number of patients (n) with an increase in pain score is presented for each treatment group. Baseline scores of 0 are imputed with a value of 0.00001 to enable calculation of percent change.

NGL Naloxegol; NRS Numeric Rating Scale.

Figure 10 Percentage of patients by percent increase in weekly opioid dose, Weeks 1 to 12 (Studies K4 and K5)



Note: Opioid dose is the mean of daily maintenance and breakthrough opioid doses per week. The y-axis presents the number of patients meeting the specific percentage increase from baseline score (x-axis) divided by the number (N) of patients with baseline and post-baseline assessments for each treatment group. The total number of patients (n) with an increase in opioid dose is presented for each treatment group.

NGL Naloxegol.

12.6 By-patient listing tables for key safety parameters

12.6.1 Deaths in the naloxegol development program

Table 26 provides a by-patient summary of each of the 7 deaths reported in the naloxegol clinical program.

Table 26 Key information regarding AEs with outcome of death during the treatment period or post-treatment follow-up

Study	Treatment	Age/race/sex	Relevant history and description of AE	Preferred term	Exposure (days)/ Completed study (yes/no)	Time from last dose (days)
Phase I Study 9	NGL 25 mg	60-64 y/W/M	History of severe renal impairment, CHF, hypertension, and DM (patient was not treated with opioids) MI SAE on Day 18, 17 days following a single 25-mg dose CABG performed on Day 25 Post-surgical pericarditis, atrial fibrillation, and pneumonia; hemodialysis started during hospitalization; discharged 14 days after being admitted; died of sudden cardiac death on Day 35 Opioids: None	Myocardial infarction	1/No	35
Phase II	NGL 25 mg	55-59 y/W/F	History of recurrent DVT; post-inferior vena cava filter placement Sudden death without previous signs or symptoms of acute illness A post mortem biopsy was performed, confirming pulmonary embolism Opioids: morphine, hydrocodone	Pulmonary embolism	6/No	3
Study K8	Usual Care	30-34 y/W/F	History of anxiety, ADHD, and personality disorder Patient died unobserved while asleep on Day 95 Opioids: at baseline, hydromorphone 8 mg TID and oxymorphone hydrochloride 10 mg BID (total 165.0 meu); on Day 7, oxymorphone hydrochloride was increased to 20 mg BID	Death	95/No	1
Study K4	NGL 12.5 mg	55-59 y/W/F	History of pneumonia and COPD Pneumonia SAE on Day 102; NSCLC SAE on Day 109 Follow-up suggestive of a pre-existing lung cancer Opioid: oxycodone (450.0 meu)	Non-small cell lung cancer	91/No	23

Table 26 Key information regarding AEs with outcome of death during the treatment period or post-treatment follow-up

Study	Treatment	Age/race/sex	Relevant history and description of AE	Preferred term	Exposure (days)/ Completed study (yes/no)	Time from last dose (days)
Study K4	NGL 12.5 mg	70-74 y/W/M	History of hyperlipidemia, hypertension, IDDM, CAD s/p coronary stent placement, past smoker/drinker Acute MI SAE on Day 16 with concurrent atrial fibrillation (presenting event) Underwent CABG/AVR; post-operative pneumonia, sepsis, and renal failure; transferred to a nursing facility where he later died Opioids: hydrocodone+paracetamol and tramadol hydrochloride (total 296.6 meu)	Cardiac valve replacement complication	16/No	34
Study K7	NGL 12.5 mg	50-54 y/W/M	History of DM (with retinopathy), hyperlipidemia, and hypertension Road traffic accident SAE (in conjunction with hyperglycemia) on Day 60; left hospital on the same day; died unobserved on the following day Opioids: oxycodone hydrochloride and oxycodone+paracetamol (total 135.0 meu)	Myocardial ischaemia	141/No	6
Study K8	NGL 25 mg	35-39 y/W/F	No relevant history Idiopathic generalized epilepsy SAE on Day 111 Autopsy findings revealed pulmonary congestion and edema Opioids: oxycodone+paracetamol (total 30.0 meu)	Idiopathic generalized epilepsy	92/No	20

ADHD Attention-deficit/hyperactivity disorder; AE Adverse event; AVR Aortic valve replacement; BID Twice daily; CABG Coronary artery bypass grafting; CAD Coronary artery disease; CHF Congestive heart failure; COPD Chronic obstructive pulmonary disease; DM Diabetes mellitus; DVT Deep vein thrombosis; F Female; IDDM Insulin-dependent diabetes mellitus; M Male; meu Morphine equivalent units; MI Myocardial infarction; NSCLC Non-small cell lung carcinoma; SAE Serious adverse event; s/p Status post; TID 3 times daily; W White; y Years.

12.6.2 Patients with Investigator-reported opioid withdrawal adverse events in the naloxegol Phase III program

A summary of the 13 patients with opioid withdrawal (OWD) adverse events (AEs) in the Phase III studies is presented in Table 27. A summary table of blood pressure and pulse rate for each of the 7 patients with attributable OWD AEs is provided in Table 28.

Table 27 Summary of patients with AEs of OWD

Age/race/sex Study Opioid	Onset Outcome	Completed the Study?	Intensity/SAE/DAE	OWD symptoms reported in the study[a]	Comments
Cases attributable to investigational product					
Placebo					
40-44 y/W/F Study K4 Morphine, oxycodone, and acetaminophen	Day 01 Resolved Day 10	No	Moderate/DAE	Piloerection, sweating, and agitation	Positive rechallenge
Naloxegol 12.5 mg					
45-49 y/W/F Study K4 Oxycodone	Day 03 Resolved Day 10	Yes	Mild	Yawning, teariness, runny nose, and flushing	None
Naloxegol 25 mg					
60-64 y/W/M Study K4 Methadone	Day 01 Resolved Day 2	No	Moderate	Diarrhea and abdominal cramping, piloerection, sweating, shakiness, anxiety, increased pain, nasal congestion, and dilated pupils	Naloxegol discontinued on Day 01 due to diarrhea
65-69 y/W/F Study K5 Morphine	Day 02 Resolved Day 22	No	Mild	Diarrhea, flatulence, and nausea; cold sweats and watery eyes	Positive rechallenge
55-59 y/B/F Study K5 Methadone and tramadol	Day 01 Resolved Day 01	No	Moderate/DAE	Abdominal cramps and vomiting; yawning, chills, rhinorrhea, piloerection, and tremulousness	None
30-34 y/W/F Study K5 Methadone	Day 01 Resolved Day 03	Yes	Severe	Severe abdominal pain, mild flatulence, and severe vomiting; lacrimation, yawning, piloerection, sweating, and chills	mHS increased from 0 at pre-dose to 5 post-dose; positive rechallenge

Table 27 Summary of patients with AEs of OWD

Age/race/sex Study Opioid	Onset Outcome	Completed the Study?	Intensity/SAE/DAE	OWD symptoms reported in the study[a]	Comments
45-49 y/W/F Study K5 Methadone	Day 01 Resolved Day 05	Yes	Moderate	Abdominal pain and vomiting; lacrimation, yawning, piloerection, and tremors	mHS increased from 0 at pre-dose to 8 post-dose
Cases not attributable to investigational product					
Naloxegol 12.5 mg					
55-59 y/B/M Study K5 Oxycodone	Day 83 Resolved Day 85	Yes	Mild	Diarrhea, rhinorrhea, piloerection, and restlessness	Patient ran out of opioid 2 days prior to the event. mHS increased from 0 prior to the event to 3 on Day 85
60-64 y/W/F Study K7 Hydrocodone	Day 101 Resolved Day 112	No	Moderate/SAE	Diarrhea, piloerection, tremor, and restlessness	Patient stopped opioid and naloxegol 3 days prior to AE of OWD. Concurrent AE of diarrhea that led to discontinuation; restarted opioid on Day 109
Naloxegol 25 mg					
65-69 y/W/M Study K7 Morphine	Day 153 Resolved Day 154	No	Mild/SAE/DAE	None reported	Patient had an SAE of altered mental status and AEs of left-sided facial swelling and pain from dental procedure. Mental status change was suspected to result from morphine, which was stopped. In addition, patient was given naloxone to reverse morphine's effects.

Table 27 Summary of patients with AEs of OWD

Age/race/sex Study Opioid	Onset Outcome	Completed the Study?	Intensity/SAE/DAE	OWD symptoms reported in the study[a]	Comments
45-49 y/B/F Study K8 Morphine	Day 365 Resolved Day 377	Yes	Mild	None reported	Event took place after the final treatment visit and last dose of naloxegol on Day 362.
45-49 y/W/F Study K8 Morphine	Day 11 Resolved Day 15	No	Severe	None reported	Morphine dose was decreased at the patient's request.
60-64 y/W/F Study K8 Oxycodone with acetaminophen	Day 34 Resolved Day 48	No	Severe	None reported	Patient ran out of narcotic for 2 weeks. Resumed narcotic on Day 48.

[a] Includes additional information reported by the Investigator and not captured as individual AEs.

AE Adverse event; B Black; DAE Discontinuation of investigational product due to an adverse event; F Female; M Male; mHS Modified Himmelsbach scale; OWD Opioid withdrawal; SAE Serious adverse event; W White; y Years.

Table 28 Summary of blood pressure and pulse in patients with attributable AEs of OWD

			Blood pressure (mmHg)			Pulse rate (bpm)		
Study/Treatment	**Age/sex**	**Event onset (Day)**	**Day 1 Pre-dose**	**Day 1 Post-dose**	**Week 1**	**Day 1 Pre-dose**	**Day 1 Post-dose**	**Week 1**
Study K4/PBO	40-44/F	1	122/80	112/74	112/76	76	80	NA
Study K4/12.5 mg	45-49/F	3	124/82	122/78	120/80	88	88	84
Study K4/25 mg	60-64/M	1	116/66	110/66	112/62	60	64	60
Study K5/25 mg	65-69/F	2	160/90	154/80	142/80 (Day 3) 154/82 (Day 8)	60	58	62 (Day 3) 60 (Day 8)
Study K5/25 mg	55-59/F	1	114/67	113/69	112/68	82	76	76
Study K5/25 mg	30-35/F	1	115/65	114/68	99/55 (Day 2) 122/56 (Day 5) 106/64 (Day 7)	73	80	75 (Day 2) 76 (Day 5) 68 (Day 7)
Study K5/25 mg	45-49/F	1	123/78	143/79	118/62 (Day 3) 124/67 (Day 8)	74	74	80 (Day 3) 70 (Day 8)

AE Adverse event; bpm Beats per minute; F Female; M Male; NA Not available; OWD Opioid withdrawal; PBO Placebo.

12.6.3 Patients meeting the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)-based criteria for OWD in the naloxegol Phase III program

Details for each of the 6 patients who had ≥3 concurrent AEs listed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a symptom of OWD are provided in Table 29. To be programmatically identified as meeting the DSM-5 criteria, a patient had to have these 3 separate AEs within a 7-day window at any time during the study.

Table 29 Key information for patients with at least 3 AEs listed as OWD symptoms in the DSM-5 that occurred within a 7-day window at any time during treatment

Age/race/sex Study Opioid	Concurrent AEs (onset)	Completed the study?	SAE or DAE
Naloxegol 12.5 mg			
55-59 y/W/F Study K5 Methadone, Oxycodone	Diarrhea, pyrexia, and vomiting (all Day 29)	Yes	None
45-49 y/W/F Study K5 Fentanyl, Oxycodone	Sweating, diarrhea, severe nausea, and severe vomiting (all Day 2)	Yes	None
Naloxegol 25 mg			
70-74 y/W/M Study K5 Oxycodone, Tramadol	Muscle aches (Day 2), insomnia (Day 9), and nausea (Day 9)	Yes	None
50-54 y/W/F Study K8 Morphine, Oxycodone	Muscle aches, rhinorrhea, yawning (all Day 1)	Yes	None
35-39 y/W/F Study K8 Oxycodone/ Vicodin	Diarrhea, fever, and vomiting (all Day 42)	No	None
30-34 y/W/M Study K8 Oxycodone	Diarrhea, sweating, and nausea (all Day 1)	No	Diarrhea, sweating, and nausea were all DAEs. None were SAEs.

AE Adverse event; DAE Discontinuation of investigational product due to adverse event; DSM-5 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; F Female; M Male; OWD Opioid withdrawal; SAE Serious adverse event; W White; y Years.

12.6.4 Patients with adjudicated major adverse cardiovascular events in the naloxegol Phase III program

Key information for each of the 11 patients adjudicated with either major adverse cardiovascular events or a hospitalization adjudicated as due to a cardiovascular event of interest are provided in Table 30.

Table 30 Key information regarding MACE during the treatment period or post-treatment follow-up

Age/race/sex Study/Opioid	Relevant history/description of event	Preferred term	Onset day/ Duration	CV adjudication comment
Placebo/Usual Care group				
60-64 y/Other/ M Study K5 Morphine, Oxycodone	Severe angina pectoris SAE on Day 17. History of angina, CAD, s/p 5-vessel CABG, PVD, dyslipidemia, hypertension, tricuspid valve disease, LBBB, and tobacco use. Hospital admission due to significant chest pain, shortness of breath, and sweating; troponin and CK-MB were elevated; cardiac catheterization showed “impressive underlying disease” but no indication for revascularization; patient was treated medically; SAE resolution and hospital discharge on Day 19. Dosed for 26 days and did not complete the study.	Angina pectoris	Day 17/ 3 days	Acute MI
40-44 y/W/M Study K5 Oxycodone	Severe acute MI DAE/SAE on Day 34. History of hypercholesterolemia and smoking (1/2 pack per day). Found semi-conscious and confused in bed and was hospitalized; troponin was elevated; cardiac catheterization showed mild occlusive disease; patient sensorium cleared; not overdose; based on catheterization findings, no angioplasty was performed; patient was treated medically; final diagnosis was NSTEMI; SAE resolved on Day 35; hospital discharge on Day 38. Dosed for 34 days and did not complete the study.	Acute MI	Day 34/ 2 days	Acute MI
50-54 y/W/M Study K8 Oxycodone, Tramadol	Severe congestive heart failure SAE on Day 248. History of CHF, CAD, irregular heartbeat, hypertension, asthma, and morbid obesity. Had 2- to 3-month history of worsening of chronic heart failure symptoms. At the time of admission, symptoms included shortness of breath, lower extremity edema, fatigue, wheezing, elevated BP, green sputum; hospitalized for CHF, acute asthma exacerbation, and atrial fibrillation; chest X-ray showed mild cardiomegaly, increased vascular markings, and prominent pulmonary fibrotic changes; ECHO showed dilated left ventricle with hypertrophy and dilated right ventricle; treated medically; SAE resolved and patient was discharged on Day 254; died 3.5 months after study completion; cause of death and autopsy results not available. Dosed for 364 days and completed the study.	Cardiac failure congestive	Day 248/ 7 days	Heart failure requiring hospitalization

Table 30 Key information regarding MACE during the treatment period or post-treatment follow-up

Age/race/sex Study/Opioid	Relevant history/description of event	Preferred term	Onset day/ Duration	CV adjudication comment
45-49 y/W/F Study K8 Hydrocodone	Severe ischemic cerebral infarction SAE on Day 74. History of bilateral carotid artery obstruction, post-menopause, hypertension, COPD, alcohol abuse, IV drug abuse, blood transfusion, smoking (1/2 pack per day), bipolar affective disorder. Presented with left-sided weakness and numbness after a fall at home; MRI showed right frontal lobe infarction; the patient received physiotherapy, occupational treatment, and medical treatment; noted to regain spontaneous use of left lower limb - able to ambulate with walker; final diagnosis was frontal lobe cerebral infarction; SAE resolution on Day 217; discharged Day 80. Dosed for 217 days and did not complete the study.	Ischaemic cerebral infarction	Day 74/ 144 days	Stroke
30-34 y/W/F Study K8 Hydromorphone, Oxymorphone	Cardiovascular death on Day 95. History of migraine, asthma, ADHD, personality disorder, anxiety. Patient died unobserved while asleep at home on Day 95; no further details were known, and resuscitation was not attempted; no known precipitating factors, suicidal ideation, or behavior reported to the study site; results of autopsy not available; unable to obtain further information despite multiple attempts. Dosed for 95 days and did not complete the study.	Death	Day 95/ 1 day	CV death
Naloxegol 12.5 mg group				
70-74 y/W/M Study K4 Hydrocodone, Tramadol	Acute MI on Day 16; cardiovascular death on Day 49. History of CAD s/p coronary stent placement, hypertension, hyperlipidemia, Type 1 diabetes, and smoking. Hospitalized on Day 16 due to atrial fibrillation and ST elevation by ECG; troponin increased; diagnosed with NSTEMI; cardiac catheterization showed diffuse CAD; ECHO showed severe AS; underwent CABG/AVR; complicated post-operative course - pneumonia, sepsis, and renal failure; patient became comatose; EEG showed severe slowing; transferred to a nursing facility Day 44; patient died on Day 49. Dosed for 16 days and did not complete the study.	Cardiac valve replacement complication	Day 19/ 31 days	CV death

Table 30 Key information regarding MACE during the treatment period or post-treatment follow-up

Age/race/sex Study/Opioid	Relevant history/description of event	Preferred term	Onset day/ Duration	CV adjudication comment
50-54 y/W/M Study K7 Oxycodone	Cardiovascular death on Day 146. Type 2 diabetes with retinopathy, hyperlipidemia, hypertension, GERD, ankylosing spondylitis, and depression. Patient involved in head-on traffic accident (in conjunction with hyperglycemia) on Day 145; apparently uninjured; left hospital on same day against medical advice; died unobserved on the following day; autopsy performed; cause of death attributed to IHD secondary to CAD. Dosed for 141 days and did not complete the study.	Myocardial ischaemia	Day 146/ 1 day	CV death
Naloxegol 25 mg group				
40-44 y/W/M Study K4 Hydrocodone	Acute MI DAE/SAE on Day 1. History of untreated and uncontrolled hypertension, hyperlipidemia, limited activity level, obesity, smoking (2 packs per day), and excessive consumption of energy drinks. BP elevated at study screening (160/82 mmHg). Two hours after the first dose of study drug, smoking and ingestion of an energy drink, patient noted severe chest pain and elevated BP of 162/116 mmHg (pre-dose BP 162/98 mmHg). ECG - inferior ST segment elevation; nitroglycerin and oxygen relieved pain; chest pain recurred in ER, BP 164/120 mmHg, and ECG suggested inferior MI; hospitalized and cardiac catheterization revealed 95% to 100% RCA occlusion; stent successfully placed; no residual wall motion abnormalities noted; SAE resolved and discharged on Day 3. Eight months after study discontinuation, the patient was reported to have died during hospitalization, apparently related to Type B aortic dissection, hypoxic respiratory failure, and renal failure. Dosed for 1 day and did not complete the study.	MI	Day 1/ 3 days	Acute MI

Table 30 Key information regarding MACE during the treatment period or post-treatment follow-up

Age/race/sex Study/Opioid	Relevant history/description of event	Preferred term	Onset day/ Duration	CV adjudication comment
65-69 y/W/F Study K7 Hydrocodone	Severe congestive heart failure SAE on Day 118. History of CAD s/p angioplasty x 5, cardiac stent placement x 3, hypercholesterolemia, hypertension, peripheral neuropathy, small cell lung cancer (stage unknown) treated with radiochemotherapy. Hospitalized on Day 111 due to sepsis, pneumonia, and staphylococcal bacteremia; study drug discontinued on Day 112; discharged against medical advice on Day 114; readmitted on Day 118 due to CHF and pleural effusion; cardiac catheterization showed non-obstructive CAD and mild pulmonary hypertension; ECHO showed no valve vegetations; underwent right thoracentesis; SAE resolution and hospital discharge on Day 120; final diagnoses included CHF, pleural effusion, aortic insufficiency, pulmonary hypertension, and *Staphylococcus aureus* bacteremia. Dosed for 112 days and did not complete the study.	Cardiac failure congestive	Day 118/ 3 days	Heart failure requiring hospitalization
35-39 y/W/F Study K8 Oxycodone	Cardiovascular death on Day 111. Headache and back pain; no cardiovascular or neurological disorders reported or known. Patient reported to site as deceased (details not available); autopsy performed - findings revealed pulmonary congestion and edema; death certificate stated idiopathic generalized epilepsy as the cause of death; the patient had not reported a history of seizures, seizure medications, or neurologic diseases and had not reported risk factors such as meningitis or head trauma during the study; documented as not having taken study drug for approximately 20 days before the event. Dosed for 92 days and did not complete the study.	Idiopathic generalized epilepsy	Day 111/ 1 day	CV death

Table 30 Key information regarding MACE during the treatment period or post-treatment follow-up

Age/race/sex Study/Opioid	Relevant history/description of event	Preferred term	Onset day/ Duration	CV adjudication comment
55-59 y/B/F Study K8 Codeine, Oxycodone	Acute MI SAE on Day 156. History of obesity, hyperlipidemia, asthma, bipolar disorder, osteoarthritis, GERD, anemia, and intake of diet pills beyond recommended dose. Presented to ER with altered level of consciousness, confusion, and twitching; hospitalized with diagnoses of acute renal injury, rhabdomyolysis, transaminase elevations, hyperkalemia, and elevated troponin attributed to overuse of diet pill; treated medically with resolution of SAE and hospital discharge on Day 160. Dosed for 166 days and did not complete the study.	Troponin increased	Day 156/ 5 days	Acute MI

Note: No mHS and NRS data from the time of the events of these cases are available.

Note: Other race category: Asian, Native Hawaiian or Pacific Islander, American Indian or Alaska native, Other.

ADHD Attention-deficit/hyperactivity disorder; AVR Aortic valve replacement; B Black, BP Blood pressure; CABG Coronary artery bypass grafting; CAD Coronary artery disease; CHF Congestive heart failure; CK-MB Creatine phosphokinase MB isoenzyme; COPD Chronic obstructive pulmonary disease; CV Cardiovascular; DAE Discontinuation of investigational product due to an adverse event; ECG Electrocardiogram; ECHO Echocardiogram; EEG Electroencephalogram; ER Emergency room; F Female; GERD Gastroesophageal reflux disease; IHD Ischemic heart disease; IV Intravenous; LBBB Left bundle branch block; M Male; MACE Major adverse cardiovascular event; mHS modified Himmelsbach scale; MI Myocardial infarction; MRI Magnetic resonance imaging; NRS Numeric Rating Scale; NSTEMI Non-ST elevated myocardial infarction; PVD Peripheral vascular disease; RCA Right coronary artery; SAE Serious adverse event; s/p Status post; W White; y Years.

12.6.5 Patients with syncope AEs in the naloxegol Phase III program

Table 31 Key information regarding syncope events during the treatment period or post-treatment follow-up

Age/race/sex Study Opioid	Onset Outcome	Completed the Study?	Exposure (days)	SAE/DAE	CV History/Con Meds	Clinical information
Naloxegol 12.5 mg						
35-39 y/W/F Study K4 Hydrocodone	Day 35 Resolved Day 37	No (withdrawn from study on Day 127)	35	Yes/Yes	HTN, obesity, CV risk: high/ Lisinopril, HCTZ	Relevant AEs prior to event: dehydration, hypokalemia (4 mmol/L, Day 42), hyponatremia (137 mmol/L, Day 42), hypotension (84/48 mmHg), nausea (Day 35). Lab results from site visit not ER. Subject had 2 episodes of syncope. The second (SAE) was while holding a glass coffee pot. Subject passed out, broke the coffee pot and sustained injury. Subject presented to ER dehydrated, dizziness, hyponatremia, hypokalemia, nausea, orthostatic hypotension. BP: Baseline 94/66 mmHg, on AE 84/48 mmHg. No OWD symptom at the time of AE.
50-54 y/W/M Study K5 Oxycodone	Day 43 Resolved Day 43	Yes	86	Yes/No	HTN, hypercholesterolemia, DM1, CV risk: high/ N/A	Relevant AE prior to event: lightheaded, dizzy, abdominal pain (Days 1 to 32). While getting off toilet at home, patient felt lightheaded, dizzy and had vasovagal syncope (SAE), fell and was injured. BP: Baseline 108/70 mmHg, on AE N/A. No OWD symptom at the time of AE.
Naloxegol 25 mg						
60-64 y/W/M Study K5 Tramadol, Codeine	Day 60 Resolved Day 60	Yes	85	No/No	Syncope, HTN, hypercholesterolemia, CV risk: high/ N/A	Relevant AE prior to event: Abdominal pain (Days 28 to 98). On Day 60, patient had syncope. Patient presented with paleness, incontinence, hypotension, and diaphoresis. Blood pressure at the time of AE was 93/50 mmHg and pulse of 80 bpm (body position unspecified). AE required treatment with “IV medication fluids” (medication name and dose unspecified). BP: Baseline: 116/69 mmHg, on AE 93/50 mmHg. No OWD symptom at the time of AE.

Table 31 Key information regarding syncope events during the treatment period or post-treatment follow-up

Age/race/sex Study Opioid	Onset Outcome	Completed the Study?	Exposure (days)	SAE/DAE	CV History/Con Meds	Clinical information
55-59 y/W/F Study K8 Hydrocodone	Day 249 Resolved Day 253	No (withdrawn from study on Day 267)	249	Yes/Yes	HTN, hypotension, obesity, CV risk: high / Lisinopril	Relevant AEs prior to event: dizzy, hypertension (Days 90 to 267). On Day 249, patient went to bathroom, suddenly felt dizzy and fell/passed out and hurt her back. She was helped by her husband and fell/passed out again. She was hospitalized for syncope (SAE). Per the patient, she had a history of low BP and was recently diagnosed with HTN. ECHO, duplex carotid bilateral scan, CT of head without contrast, chest X-ray, and cervical/thoracic/lumbar spine X-ray were normal. CBC count and cardiac biomarkers were normal; chemistry panel showed high calcium, protein, glucose and low anion gap. BP: Baseline 102/69 mmHg, on AE 99/49 mmHg. No OWD symptom at the time of AE.
50-54 y/W/M Study K8 Oxycodone	Day 133 Resolved Day 134	Yes	361	No/No	HTN, cardiac murmur, hyperlipidemia. CV risk: high/ Nifedipine, quinapril	Relevant AE prior to event: hypertension and cardiac murmur. On Day 133, patient slipped and fell on a broken ceramic tile floor while at home. An episode of syncope (not witnessed) occurred after the patient fell and while he attempted to ambulate with fractured tibia and fibula. The emergency services were called, and the patient was transferred to hospital where it was confirmed the patient had a displaced distal third tibia fracture and right fractured fibula. Blood pressure surrounding the event was not available. BP: Baseline 105/72 mmHg, on AE N/A. No OWD symptom at the time of AE.

Table 31 Key information regarding syncope events during the treatment period or post-treatment follow-up

Age/race/sex Study Opioid	Onset Outcome	Completed the Study?	Exposure (days)	SAE/DAE	CV History/Con Meds	Clinical information
60-64 y/W/F Study K8 Morphine, oxycodone	Day 3 Resolved Day 5	No (withdrawn from study on Day 58)	3	No/Yes	Dilatation ventricular, HTN. CV risk: high/ Flomax	Relevant AE prior to event: urinary hesitation, and urinary retention (Days 3 to 8). Patient had a moderate DAE of syncope, not witnessed, on Day 3. Patient did not go to hospital, ER, and urgent care and was not dehydrated or hypovolemic. Per the site, "syncope was thought to be related as a side effect to Flomax used to treat urinary retention, and not related to IP by the investigator.” BP: Baseline 102/62 mmHg, on AE N/A. No OWD symptom at the time of AE.

AE Adverse event; BP Blood pressure; bpm Beats per minute; CBC count Complete blood cell count; Con Meds Concomitant medications; CT Computed tomography; CV Cardiovascular; DAE Discontinuation of investigational product due to an adverse event; DM1 Diabetes mellitus type 1; ECHO Echocardiogram; ER Emergency room; F Female; HCTZ Hydrochlorothiazide; HTN Hypertension; IP Investigational product; IV Intravenous; M Male; N/A Not applicable; OWD Opioid withdrawal syndrome; SAE Serious adverse event; W White; y Years.

12.7 Vital sign changes

This appendix includes a summary table of mean changes from baseline for vital signs and values outside AstraZeneca's standard threshold values, and bar graphs of systolic blood pressure and pulse rate changes from baseline at the 1-hour post-dose time point.

Table 32 Summary of mean changes from baseline for vital signs and values outside AstraZeneca's standard threshold values (12-week pool and Study K8)

Parameter	Category or criterion	12-week pool (Studies K4 and K5)			52-week safety study (Study K8)[a]	
		Placebo	NGL 12.5 mg	NGL 25 mg	Usual Care	NGL 25 mg
Mean change from baseline to 1 hour after first dose						
N		443	439	446	231	477
SBP (mmHg)	Mean (SD)	1.3 (9.6)	0.7 (9.0)	1.6 (10.3)	1.5 (8.6)	2.1 (10.0)
DBP (mmHg)	Mean (SD)	-0.1 (6.8)	0.7 (6.3)	0.7 (6.9)	0.2 (6.4)	0.5 (6.8)
Pulse (bpm)	Mean (SD)	-2.7 (6.6)	-2.5 (7.3)	-2.4 (7.5)[b]	-1.1 (8.2)	-2.6 (7.4)
Mean change from baseline to last on-treatment						
N		444	441	446	234	481
SBP (mmHg)	Mean (SD)	0.8 (14.4)	0.4 (12.9)	1.3 (13.8)	0.1 (14.1)	2.3 (13.9)
DBP (mmHg)	Mean (SD)	-0.2 (9.3)	-0.2 (8.6)	0.6 (9.3)	-0.9 (10.4)	0.5 (9.1)
Pulse (bpm)	Mean (SD)	1.3 (10.3)	1.8 (10.0)	1.0 (10.6)[b]	2.0 (12.4)	1.0 (11.3)
SBP						
1 hour post-dose	n	443	439	446	231	477
	≤100 and ↓ ≥20	1 (<1%)	3 (<1%)	3 (<1%)	0	0
	≤100	26 (6%)	24 (5%)	24 (5%)	10 (4%)	15 (3%)
	↓ ≥20	6 (1%)	8 (2%)	9 (2%)	1 (<1%)	8 (2%)
	≥160 and ↑ ≥20	2 (<1%)	2 (<1%)	4 (1%)	2 (1%)	3 (<1%)
	≥160	5 (1%)	7 (2%)	13 (3%)	6 (3%)	7 (1%)
	↑ ≥20	17 (4%)	14 (3%)	28 (6%)	7 (3%)	26 (5%)
On-treatment	n	444	441	446	234	481
	≤100 and ↓ ≥20	18 (4%)	27 (6%)	17 (4%)	14 (6%)	28 (6%)
	≤100	66 (15%)	72 (16%)	71 (16%)	37 (16%)	85 (18%)
	↓ ≥20	68 (15%)	80 (18%)	59 (13%)	49 (21%)	88 (18%)
	≥160 and ↑ ≥20	14 (3%)	17 (4%)	13 (3%)	18 (8%)	18 (4%)
	≥160	19 (4%)	24 (5%)	23 (5%)	20 (9%)	28 (6%)
	↑ ≥20	95 (21%)	80 (18%)	101 (23%)	61 (26%)	131 (27%)

Table 32 Summary of mean changes from baseline for vital signs and values outside AstraZeneca's standard threshold values (12-week pool and Study K8)

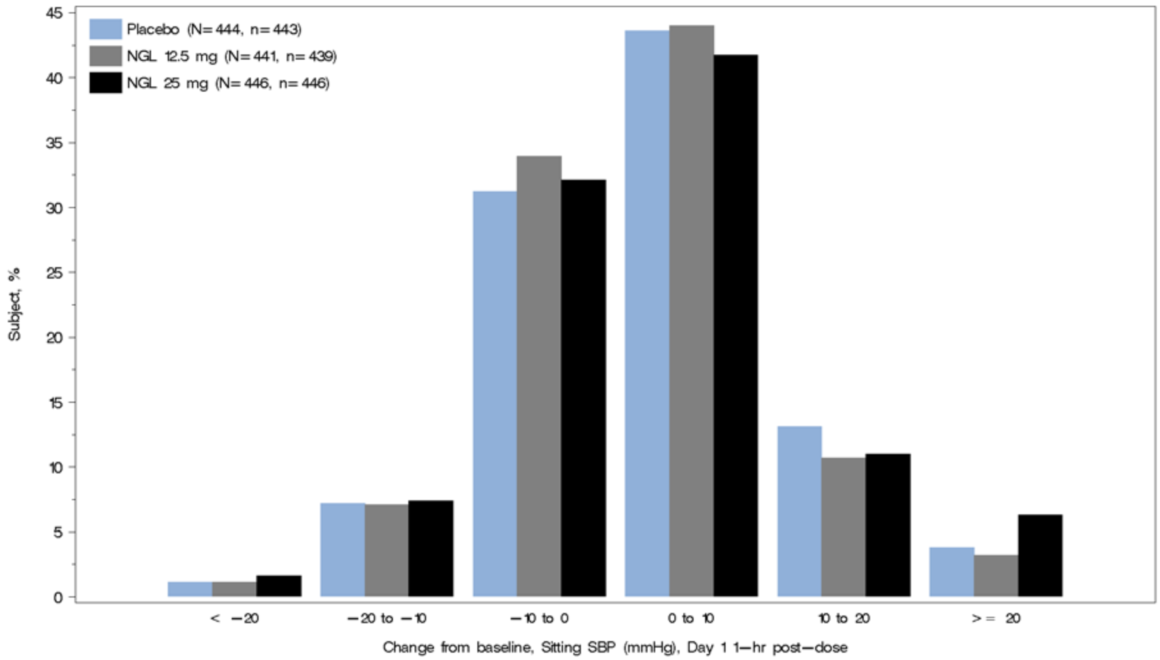
Parameter	Category or criterion	12-week pool (Studies K4 and K5)			52-week safety study (Study K8)[a]	
		Placebo	NGL 12.5 mg	NGL 25 mg	Usual Care	NGL 25 mg
DBP						
1 hour post-dose	n	443	439	446	231	477
	≤50 and ↓ ≥10	2 (<1%)	0	1 (<1%)	1 (<1%)	0
	≤50	6 (1%)	0	2 (<1%)	2 (<1%)	1 (<1%)
	↓ ≥10	31 (7%)	27 (6%)	28 (6%)	14 (6%)	30 (6%)
	≥95 and ↑ ≥10	5 (1%)	8 (2%)	6 (1%)	2 (1%)	5 (1%)
	≥95	15 (3%)	18 (4%)	19 (4%)	10 (4%)	16 (3%)
	↑ ≥10	28 (6%)	36 (8%)	41 (9%)	14 (6%)	40 (8%)
On-treatment	n	444	441	446	234	481
	≤50 and ↓ ≥10	4 (<1%)	2 (<1%)	7 (2%)	5 (2%)	2 (<1%)
	≤50	10 (2%)	3 (<1%)	10 (2%)	7 (3%)	5 (1%)
	↓ ≥10	148 (33%)	158 (36%)	147(33%)	92 (39%)	169(35%)
	≥95 and ≥10 ↑	44 (10%)	34 (8%)	30 (7%)	23 (10%)	35 (7%)
	≥95	62 (14%)	54 (12%)	51 (11%)	35 (15%)	51 (11%)
	≥10 ↑	165 (37%)	147 (33%)	148(33%)	95 (41%)	177(37%)
Pulse rate						
1 hour post-dose	n	443	439	445	231	477
	≤50 and ↓ ≥20	1 (<1%)	0	0	0	0
	≤50	7 (2%)	7 (2%)	10 (2%)	6 (3%)	7 (1%)
	↓ ≥20	6 (1%)	8 (2%)	12 (3%)	5 (3%)	12 (2%)
	≥100 and ↑ ≥20	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)
	≥100	5 (1%)	6 (1%)	9 (2%)	3 (1%)	4 (<1%)
	↑ ≥20	1 (<1%)	2 (<1%)	2 (<1%)	4 (2%)	1 (<1%)
On-treatment	n	444	441	446	234	481
	≤50 and ↓ ≥20	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
	≤50	18 (4%)	11 (2%)	16 (4%)	15 (6%)	15 (3%)
	↓ ≥20	21 (5%)	28 (6%)	41 (9%)	24 (10%)	44 (9%)
	≥100 and ↑ ≥20	14 (3%)	11 (2%)	10 (2%)	13 (6%)	24 (5%)
	≥100	31 (7%)	33 (7%)	33 (7%)	21 (9%)	49 (10%)
	↑ ≥20	49 (11%)	64 (15%)	56 (13%)	45 (19%)	78 (16%)

[a] For Study K8, only patients who had not previously participated in a naloxegol study, approximately 90% of the study population, are included.

[b] N=445 for this assessment.

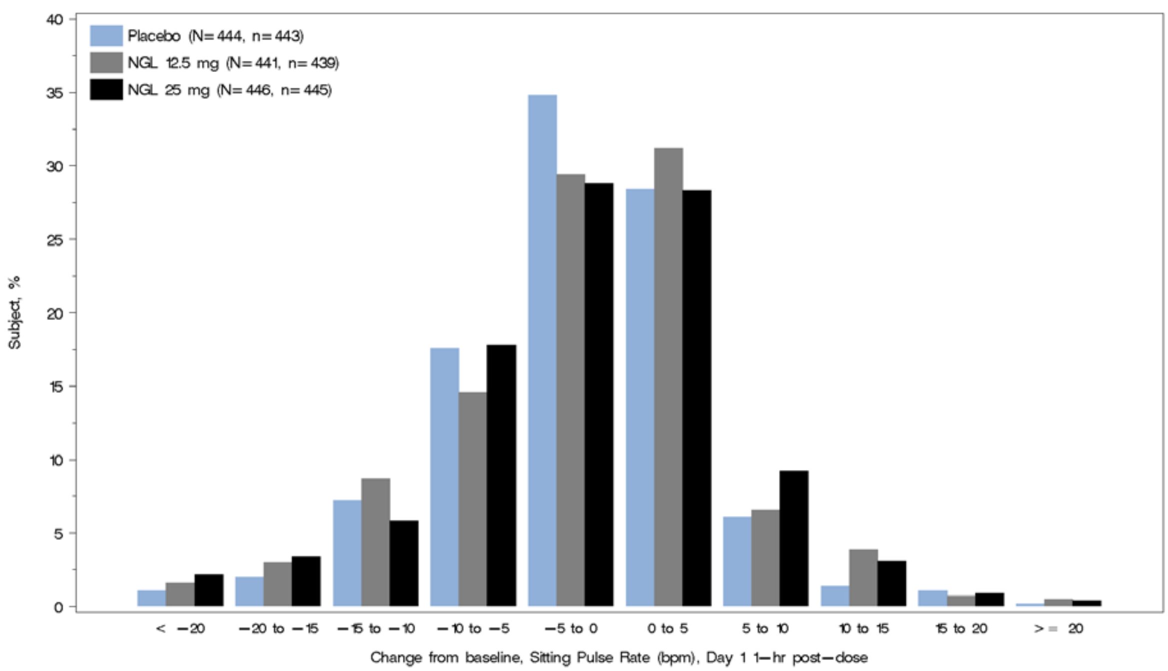
bpm Beats per minute; DBP Diastolic blood pressure; N Number of patients in safety population; n Number of patients in category; NGL Naloxegol; SBP Systolic blood pressure; SD Standard deviation.

Figure 11 Change from baseline in sitting systolic blood pressure (mmHg), 1 hour after first dose (Studies K4 and K5)



Categories include the lower limit of the interval (eg, 0 to 10 means >= 0 to < 10). The denominator for the percentages is the number of patients (n) with both a non−missing baseline value and a non−missing value at respective assessment.

Figure 12 Change from baseline in sitting pulse (bpm), 1 hour after first dose (Studies K4 and K5)



Categories include the lower limit of the interval (eg, 0 to 10 means >= 0 to < 10). The denominator for the percentages is the number of patients (n) with both a non−missing baseline value and a non−missing value at respective assessment.

12.8 List of DSM-5 AE terms

OWD syndrome is typically a flu-like, non-life-threatening condition. As defined in the DSM-5(American Psychiatric Association 2013), OWD is defined as follows (all 4 criteria, A, B, C, and D must apply):

A. **Either** of the following:

- Cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer)
- Administration of an opioid antagonist after a period of opioid use

B. **Three (or more)** of the following, developing within minutes to several days after Criterion A:

- Dysphoric mood
- Nausea or vomiting
- Muscle aches
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection, or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

The AE preferred terms corresponding to the DSM-5 symptoms are listed in Table 33. Three distinct symptoms will be considered “concurrent” if they all occurred (ie, had their onset) within 7 days of each other. This is equivalent to having a moving window of 7 days and counting the number of distinct symptoms within the window and checking if the count is ≥3.

Table 33 DSM-5 symptoms and corresponding adverse event preferred terms

Symptoms	Corresponding adverse event preferred terms
Dysphoric mood	Agitated depression; Depressed mood; Depression; Dysphoria; Depressive symptom
Nausea or vomiting	Nausea; Vomiting
Muscle aches	Myalgia
Lacrimation or rhinorrhea	Lacrimation increased; Rhinorrhoea; Rhinitis
Pupillary dilation, piloerection, or sweating	Mydriasis; Piloerection; Hyperhidrosis; Night sweats; Cold sweat
Diarrhea	Diarrhoea
Yawning	Yawning
Fever	Pyrexia
Insomnia	Insomnia, initial insomnia

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